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Original Communications

THE DIGITAL ARTERIOLES OF NORMAL AND HYPERTENSIVE INDIVIDUALS

Their Response to Intravenous Administration of Epinephrine, as Measured by Cutaneous Temperature*

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IT IS now fairly well established that the response of the blood pressure to certain stimuli is greater among subjects who have essential hypertension than it is among most individuals who do not have hypertension. Thus, pain,[1] inhalation of carbon dioxide,[2, 3] exercise,[4] psychic disturbances,[5] and immersion of the hand in ice water[6] are known to produce an exaggerated response in the blood pressure of individuals who have essential hypertension.

While it is true that most individuals who do not have hypertension do not respond abnormally to these stimuli, it nevertheless is a well-known fact that some normal individuals do respond abnormally. To this group of individuals Hines and Brown,[6] on the basis of the response of the blood pressure to the cold pressor test, have applied the appellation "normal hyperreactors." According to the manner in which their blood pressure reacts to the cold pressor test, individuals may be divided into three groups; (1) normal individuals, or individuals whose blood pressure is normal and whose response to the cold pressor test is minimal; (2) hyperreactive normal individuals, or individuals who have a normal blood pressure but react abnormally to the cold pressor test; (3) hypertensive individuals, or those who have clinical evidence of hypertension and who practically always react abnormally to the cold pressor test.

The observations of Hardgrove, Roth, and Brown[3] have demonstrated that the response of the blood pressure of these three groups of individuals to inhalation of carbon dioxide parallels the response to the cold pressor test.

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It should be clearly stated in the beginning that it is not the purpose of this paper to attempt to establish any etiological relationship between the hyperreactivity of the vasomotor system to the stimuli previously mentioned and the hypertensive state. However, aside from any etiological significance that might exist, it appears to us that this phenomenon is most certainly of sufficient importance to warrant investigation of the mechanism which produces it. The work reported in this paper was undertaken in the hope that it might throw some further light on this mechanism.

STATEMENT OF PROBLEM

The present investigation is concerned, generally speaking, with the problem of the abnormal vasopressor response to certain stimuli (cold, pain, etc.) which occurs among subjects who have essential hypertension and among certain individuals who have a normal blood pressure. It represents an attempt to determine whether or not this abnormal vasomotor response might be explained in part by the presence of an arteriolar hypersensitivity to pressor stimuli. Specifically, it is concerned with determination of the reaction of the digital arterioles to a common stimulus, epinephrine. The reaction is measured by determination of the cutaneous temperature. The types of subjects employed are divided into groups which will be explained later.

The investigations of Raab[2, 7] on this problem led him to conclude that the abnormal response of the blood pressure of hypertensive subjects to various stimuli is caused by a hyperirritability of the vasomotor centers produced by the accumulation of lactic acid within these centers. He based this conclusion on his experimental work which showed, first, that a hyperirritability of the vasomotor centers of cats to inhaled carbon dioxide resulted from a shortage of oxygen, or perfusion of the brain stem with lactic acid and, second, that a similar hyperirritability occurred among human subjects who had essential hypertension.

Apparently, very little attention has been directed toward the possibility that the peripheral vasomotor mechanism might play a part in this abnormal reaction. Lian, Stoicesco, and Vidrasco[8] by means of the plethysmograph investigated the effect of intravenous administration of a solution of epinephrine on the blood flow of the forearm of normal and hypertensive subjects and concluded, generally speaking, that there is a marked hyperexcitability of the vasomotor system of the hypertensive individual. One cubic centimeter of a 1:100,000 solution of epinephrine when administered intravenously to hypertensive subjects produces a greater rise in the blood pressure and plethysmographic evidence of a much greater peripheral vasoconstriction than it does when administered to normal individuals. This would seem to indicate that the peripheral arterioles of hypertensive

subjects are more sensitive to the epinephrine than are those of normal individuals. These authors, however, did not draw any distinction between those subjects who have a normal blood pressure and who give an abnormal vasopressor response to stimuli, such as cold and inhalation of carbon dioxide, and those who did not give such a response.

Steele and Kirk[9] did not find any significant differences in the cutaneous temperatures of normal and hypertensive subjects in rather prolonged periods.

In view of the scant attention that has been paid to the possibility that arteriolar hyperirritability to pressor stimuli may play a part in the production of this hyperreactive vasomotor mechanism, it seemed timely to make some observations in this direction. It was, therefore, decided to observe the effect of a common stimulus (epinephrine administered intravenously) on certain of the peripheral arterioles (digital) in order to determine whether or not there is any difference in the response of the arterioles of individuals who give a minimal (or normal) vasopressor response to the cold pressor test of Hines and Brown and individuals who have essential hypertension and who give an abnormal response to this test.

Epinephrine was considered a suitable substance for the investigation of this problem because its vasoconstrictor action is known to be a local one. Furthermore, as was shown by Elliott in 1905,[10] the effect of epinephrine on the arterioles is comparable to that which results from sympathetic stimulation. Cannon[11] recently has pointed out that the action of sympathetic impulses is accomplished by the liberation at the myoneural junction of a substance (sympathin) which is very similar physiologically to epinephrine. In short, epinephrine was chosen because when injected intravenously its action on the arterioles is qualitatively similar to that of sympathetic stimulation.

METHOD OF OBSERVATION

The technic used is essentially the same as that employed by Freeman, Smithwick and White[12] in their investigations of the effect of epinephrine on digital arterioles. The individuals who kindly consented to serve as subjects for these observations were brought into a room which had a fairly constant temperature (26° to 28° C.); they were allowed to lie down and expose their hands and feet for a period sufficiently long to allow the cutaneous temperature of the digits to become fairly stable (usually thirty minutes to an hour). In certain cases in which the initial temperature of the digits was too low to allow satisfactory demonstration of the vasoconstrictor action of the epinephrine, it was found necessary to elevate the cutaneous temperature by placing a heat tent, the temperature of which was kept 45-55° C., over the trunk; the hands and feet were left exposed to the room temperature. In such cases the heat tent was allowed to remain in place throughout the experiment. This was necessary because of the obvious fact that one cannot demonstrate the vasoconstrictor action of a drug when the arterioles are primarily in a state of vasoconstriction. The vasodilatation produced by the heat apparently had no inhibiting action on the vasoconstrictor effect of the epinephrine. A cutaneous temperature

of 30° C. was established as the minimal level at which the observations were made. After the temperature of the digits had reached a fairly stable level, the infusion was started. Physiological saline solution was administered for a short period; then, without the patient's knowing it, administration of a 1:250,000 solution of epinephrine was begun. This solution usually was administered for twenty to thirty minutes. The rate of the injection was sufficiently rapid (usually 3 to 9 c.c. per minute; 0.012 to 0.036 mg. of epinephrine per minute) to produce a minimal elevation of 20 mm. of mercury in the systolic blood pressure. The administration of epinephrine then was stopped and at times the physiological saline solution was allowed to run into the vein for a short period, that is, long enough as a rule to allow the temperature of the digits to regain the preinjection level. At other times, administration of the physiological saline solution and administration of the solution of epinephrine were stopped simultaneously. Such a procedure was followed for the purpose of eliminating as much as possible the psychic factors that might have influenced the cutaneous temperature had the patients known the exact moment at which the administration of epinephrine was to be started. During the entire observation the blood pressure, pulse rate, and the cutaneous temperature of the volar surfaces of the distal phalanges of several of the digits of the upper extremities were taken at intervals of three to five minutes. The observations of the cutaneous temperature were made by using a thermopile equipped with copper-constantan junctions.

INDIVIDUALS OBSERVED

Fifteen individuals were observed. These were divided into three groups: Group 1 consisted of five individuals who had normal blood pressures and reacted normally to the cold pressor test. As far as could be ascertained by physical and ophthalmoscopic examination, the individuals in this group possessed normal arteries. Group 2 consisted of three subjects who had normal blood pressures but reacted abnormally to the cold pressor test; that is, there was an increase of more than 20 mm. of mercury in the values for the systolic and diastolic pressures. Group 3 consisted of seven individuals who had clinical evidence of hypertension and reacted abnormally to the cold pressor test.

RESULTS

The vasoconstrictor effect of epinephrine was measured as the extent of the decrease in cutaneous temperature (expressed in degrees centigrade) from the preinjection level. The results have been charted in three ways: first, as the maximal decrease in digital temperature in each individual case; second, as the minimal decrease in digital temperature in each individual case; and third, as the average decrease in digital temperature in each individual case. This last value was obtained by adding the values representing the decrease in temperature of all the digits measured in an individual case and dividing this result by the number of digits measured. The results obtained are shown in Fig. 1.

Group 1.—It will be seen that in this group there was a marked variation in the decrease in cutaneous temperature; the maximal response varied from a decrease of 7.6° to 0.8° C. It also will be seen that there

is a fairly close correspondence between the degree of decrease in the temperature of the digits of any one individual.

Group 2.—Unfortunately, this group included only three subjects. This number is probably too small to justify the formation of any conclusions. However, it will be noted that here, also, as in Group 1, there were rather marked variations in the vasoconstrictor effect of epinephrine.

Group 3.—It will be seen that in this group the variations in the decrease in cutaneous temperature were practically as great as they were in Group 1; the maximal decrease varied from 7° to 1.8° C. In this group there also was a fairly close correspondence between the degree of the decrease in the cutaneous temperature of the digits of any one individual.

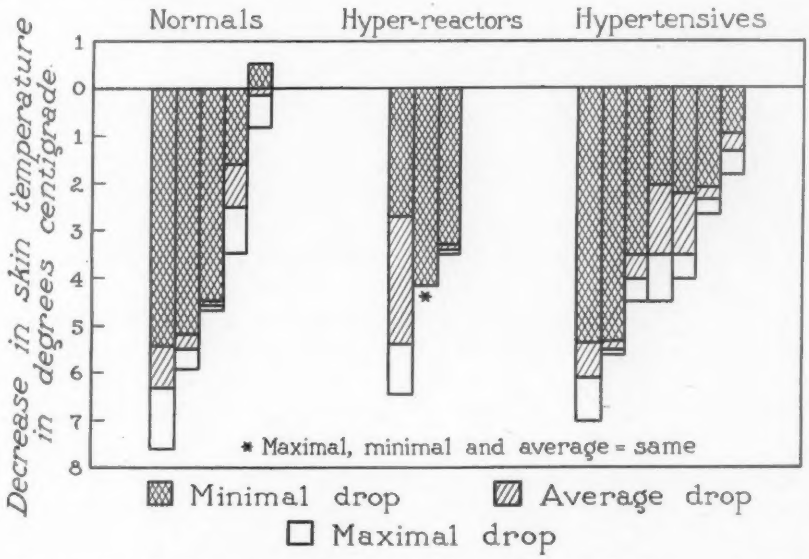

FIG. 1.—The effect of epinephrine (1:250,000), administered intravenously, on the cutaneous temperature of normal, hyperreactive normal, and hypertensive individuals.

COMMENT

From the results of these observations it becomes apparent that the vasoconstrictor effect of intravenous administration of epinephrine on the digital arterioles does not differ essentially in degree in cases in which the blood pressure is normal and responds normally to cold, and in cases of essential hypertension in which the blood pressure responds abnormally to cold.

If it can be assumed that the effect of epinephrine as administered is comparable to sympathetic stimulation, and since there is ample reason for assuming that the two are qualitatively similar at least, these experiments indicate that there is no difference in the response of the digital arterioles of normal and hypertensive subjects to sympa-

thetic impulses. In view of the fact that the action of epinephrine on the digital arterioles is similar to its action on the arterioles of the greater part of the body, it might be reasoned that in general the sensitivity of the arterioles of hypertensive individuals to pressor stimuli is no greater than is that of the arterioles of normal individuals. The limitations of our observations, however, do not justify the formation of this conclusion.

However, we do feel that these observations definitely establish the fact that there is no difference in the sensitivity of the digital arterioles of normal and hypertensive subjects to the intravenous administration of epinephrine, as measured by studies of the cutaneous temperature. It would seem that this fact rather supports the idea that in hypertension the abnormality which results in an overactivity of the vasomotor system in response to certain stimuli, such as carbon dioxide and cold, is not the result of any hypersensitivity of the arterioles to pressor stimuli, but is probably situated centrally in the vasomotor centers.

SUMMARY

The sensitivity of the digital arterioles of normal and hypertensive subjects to intravenous administration of epinephrine was investigated.

We found that there is no essential difference in the sensitivity of the arterioles of these two groups of individuals to the administration of epinephrine.

The possible relationship that the results of these observations might have to the abnormal vasomotor mechanism present in cases of hypertension has been considered.

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THE INCIDENCE AND SIGNIFICANCE OF BLOOD VESSELS IN NORMAL AND ABNORMAL HEART VALVES*

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IN A recent publication, Wearn, Bromer, and Zschiesche[1] reported the presence of vascularized valves in seventy-four of eighty-eight normal human hearts. This incidence of 84 per cent was higher than that in any previously reported series and was in complete disagreement with the findings of Gross and Kugel,[2] who stated that, if blood vessels occurred at all in noninflammatory heart valves, they were to be found only in the myocardial wedge and not in more distal portions of the valves. Inasmuch as the total number of hearts studied by Wearn, Bromer, and Zschiesche was small and the microscopic study of their material was limited, it was thought that the investigation should be extended and a more thorough and complete microscopic study be made on a larger series of hearts in order to determine the incidence of vascularized valves in normal hearts.

For more than a year, all hearts obtained at autopsy in the Institute of Pathology were injected. The method of injecting the vessels in the heart valves has been described previously by Wearn, Bromer, and Zschiesche,[1] who used India ink as an injection mass. In this study, for economical reasons, a lamp black suspension was used at first and later a 4 per cent suspension of soluble blue,‡ the latter being found to be the most suitable of the less expensive injection fluids and an excellent substitute for Berlin blue.

The results obtained with the lamp black and soluble blue differed somewhat from those obtained with India ink in the previous study and are shown in the following table:

TABLE I

	NO. OF NONINFLAMMATORY HEARTS	PER CENT WITH VESSELS IN VALVES
India ink (Weber's)	84	84%
Lamp black	120	58%
Soluble blue	135	74%

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†This investigation was carried on over a period of several years and Dr. Dowling, Dr. Haskin, Dr. Orgain, and Dr. Hudson participated in the work at one stage or another.

‡Imperial Color Works, Glen Falls, New York.

These figures include the total number of uninflamed hearts in each series, and the results with each injection material were recorded for comparison. The best efforts failed to produce an absolutely even suspension of lamp black. Small clumps of the individual particles were frequently observed when microscopic search was made for them, and it is believed that lamp black gives a lower percentage of injected vessels than does the India ink (Weber's) or soluble blue. These last two were satisfactory suspensions for the injection of capillaries.

The necessity of a clear definition of what is meant by a heart valve in this investigation is obvious. The character of the aortic and pulmonic cusps is such that no significant difference of opinion as to what constitutes "valve" can exist. The frequent extension of a myocardial wedge into the atrioventricular leaflets has led to differences of opinion as to what part of the leaflets is truly valve. A broad definition of the heart valves, and the one that we regard as correct, is that they are fibrous or fibromuscular membranes attached to the inner surface of the heart wall which, when closed, normally form an intact septum preventing the regurgitation of blood. By such a definition, the myocardial muscle wedge or even a part of the fibrous ring attachment would frequently be a part of the valve. In no instance was a valve recorded as vascularized unless vessels extended beyond a line drawn perpendicular to its surface and through the most distal point of its basal attachment.

Another definition and one which is based on the histological structure of the valve was proposed by Gross and Kugel.[2] They did not believe that the frequent extensions of the myocardium or the fibrous connective tissue from the valve ring into the center of the proximal portion of the valve should be regarded as part of the valve proper. The extent of the myocardial wedge is variable, especially in the septal leaflet of the mitral and tricuspid valves and in both situations frequently retracts with age. With the retreat of the wedge a fibrous or fibromuscular tongue often persists. It is our belief that functionally and anatomically this proximal portion of the leaflet is still valve, regardless of whether it contains myocardium or not.

Despite this academic difference as to the exact definition of a heart valve, it must be accepted that so far as the normal vascularization of the valves in relation to endocarditis is concerned, it is the distal fibroelastic portion of the valve that constitutes the significant zone.

It was not the purpose of this investigation to study the vascularization only of normal valves, but also to compare valve vascularization in inflamed and normal hearts. It is difficult to define an absolutely normal valve because of inherent developmental differences, age changes, and varying degrees of sclerosis. The macroscopic criteria

of Karsner[3] were employed in designating hearts as inflammatory or noninflammatory. These are:

1. Shortening, thickening, or adhesions between leaflets or cusps. (See subsequent discussion.)

2. The presence of active or organized vegetations.

3. Thickening, shortening, or adhesions between chordae tendineae.

There does not appear to be any justification for a reiteration of the histological features of normal valves. The question of the presence of blood vessels in normal valves will be considered later. In preparing the material for microscopic study, sections were cut from the six routine blocks of heart described by Gross and Kugel, and sufficient additional blocks were cut to include any possibly inflammatory lesions not likely to be included in the routine blocks. The sections were stained by hematoxylin and eosin, van Gieson's connective tissue method, and Verhoeff's elastic tissue method.

The recognition of inflammatory changes in valves involves a consideration of three groups of noninflammatory structural variations. The first group of variants is represented by the inherent anatomical differences in the structure of heart valves in different individuals, not related to age or disease. The examination of the heart valves of persons of comparable ages from infancy to senescence discloses striking differences in the extent of the prolongation of the myocardial wedge into the atrioventricular valves, in the number of cells, in the amount and distribution of elastic tissue, and in the amount of smooth muscle.

The second group of structural variations is related to normal age changes. The most striking of these is a change from the chondroid valve matrix of infancy to a loose fibrillar type of fibrous connective tissue with advancing age. In the case of the semilunar cusps this fibrous connective tissue becomes condensed in the arterial side of the cusp to form a fibrous zone in contrast to the loose spongy layer on the ventricular side. In the atrioventricular valves the condensation is more uniform as age advances, this being especially true in the anterior mitral leaflet. The increased density is not so much due to hyperplasia as to increased matrix density through the appearance of collagenous and hyaline material. The amount of elastic tissue increases through the first few years of life, but after five years of age there is so much normal variation in the number and thickness of elastic fibers that it is difficult to relate the variations to an aging process. Although there is great variation in the depth of the myocardial wedge in the atrioventricular leaflets, quite independent of age, there is an apparent atrophy and fibrosis of the tip of the wedge which is more striking in older individuals. In the fibrous or fibromuscular tongue, which frequently extends a considerable distance into the valve, blood vessels are likely to be numerous.

The third group of structural variations which, so far as we know, is not related to inflammation, is represented by focal degenerative changes frequently associated with calcification. These changes are commonly termed "endocardial" or "subendocardial sclerosis" and have been described in detail by Ribbert,[4] Beitzke,[5] Dewitzky,[6] and Mönckeberg.[7]

Without attempting to review the various noninflammatory degenerative changes ordinarily ascribed to sclerosis, attention must be directed to the difficulties occasionally encountered in distinguishing such changes from those due to healed endocarditis. The work of Böhmig and Krückeberg[8] illustrates the futility of attempting to establish an arbitrary distinction between healed inflammation and sclerosis of heart valves in the case of some of the borderline lesions. These investigators described nine anatomical layers in each of the atrioventricular valves and were of the opinion that in the case of localized nonexudative valve thickening, the determination of the particular layer involved is of great importance in distinguishing between inflammatory and sclerotic lesions. Such conclusions are not susceptible of proof or disproof. Obviously the possibility of an inflammation having been present in any given valve cannot be excluded. Theoretically, an inflammation can be so mild and be followed by such complete healing that either no scar is formed or, if it were formed, the scar cannot be recognized as the end-result of an inflammatory process. It does not seem likely that, even if a given indeterminate lesion could be oriented according to the nine zones of Böhmig and Krückeberg, its true identity would be any more accurately determined.

The inscriptions on the monuments to inflammation fade, and it will always remain a matter of opinion as to when they cease to be decipherable. Since this investigation had for its objective the determination of the incidence of vessels in normal valves, in contradistinction to valves that have been the seat of inflammation, the criteria for distinguishing the two must be defined. These criteria are defined with no illusions as to their infallibility and with the knowledge that certain hearts included in the normal group may have sustained a valvulitis at some remote time and that other hearts may have been excluded because of an erroneous suspicion of past inflammation. Having previously excluded all hearts in which there was shortening or adhesions between leaflets or cusps, recognizable vegetations whether they were active or healed, or shortening, thickening, or adhesions between chordae tendineae, the only microscopic ground for excluding a heart grossly accepted as noninflammatory is the finding of an active or organizing inflammatory lesion which had not been recognized on the gross examination. Fibroblastic proliferation, reduplica-

tion of elastic fibers, or the presence of thick-walled blood vessels with or without exudation, was considered acceptable microscopic evidence of inflammation.

The 333 hearts injected were divided into two groups, the first including 78 hearts which were judged to be or to have been the seat of inflammation, and the second comprised of 255 hearts regarded as being free from any stigmas of active or healed inflammation.

The percentile incidence of valve vascularization in the two groups is shown in Table II. In the inflammatory group, sixty-nine hearts, or 88 per cent of the entire group, had one or more valves vascularized. The mitral valve contained vessels most frequently, the incidence being 82 per cent, and, of the two mitral leaflets, the anterior was vascularized more commonly than the posterior in a ratio of 5 to 4. No significant differences were noted in the selective vascularization of the tricuspid leaflets or of the aortic or pulmonic cusps. The mitral was the valve most commonly affected by inflammatory changes in this series and was followed by the aortic, tricuspid, and pulmonic in diminishing frequency. Despite the fact that the pulmonic valve was least frequently the seat of valvulitis, 37 per cent of all pulmonic valves in the inflammatory group of hearts were vascularized. This represents a higher incidence of vascularization than is seen in the aortic (27 per cent), although the aortic valve was the seat of inflammation eight times as frequently as the pulmonic.

TABLE II

	PERCENTILE INCIDENCE OF VALVE VASCULARIZATION				
	MITRAL	TRICUSPID	AORTIC	PULMONIC	TOTAL
Seventy-eight hearts showing active or healed inflammation	82%	51%	27%	37%	88%
Two hundred and fifty-five hearts showing no active or healed inflammation	50%	31%	5%	14%	66%

In the noninflammatory group of 255 hearts there were 168, or 66 per cent, in which one or more valves were vascularized. The same order of frequency of valves affected was seen here as in the inflammatory group, the mitral having the highest incidence (50 per cent) followed by the tricuspid, pulmonic, and aortic in diminishing frequency. The same order of the frequency with which the various valves were vascularized was observed in the previous study by Wearn, Bromer and Zschiesche.[1]

A comparison of the inflammatory and noninflammatory groups, according to the number of valves vascularized in each heart, is shown in Table III. In the inflammatory group the vascularization of more than one valve was more common than the vascularization of a single valve in a ratio of 2 to 1. Vascularization of all four valves was seen in 17 per cent of the entire group.

In the noninflammatory group, vascularization of a single valve was more common than vascularization of more than one valve, in a ratio of 4 to 3, and in less than 1 per cent of the noninflammatory hearts were all four valves vascularized.

TABLE III

	PERCENTILE INCIDENCE OF MULTIPLE VALVE VASCULARIZATION				
	1 VALVE	2 VALVES	3 VALVES	4 VALVES	TOTAL
Seventy-eight hearts showing active or healed inflammation	28%	29%	14%	17%	88%
Two hundred and fifty-five hearts showing no active or healed inflammation	38%	22%	5%	1%	66%

The foregoing data are at variance with the observations of Gross and Kugel,[2] and it was thought that differences in the anatomical conception of what constitutes a valve might account in part for the higher incidence of vascularization of noninflammatory heart valves reported here. As stated in the early part of this paper, we chose to regard the entirety of the freely moving membranes between chambers or between the chambers and the large arteries as valve leaflets or cusps. Prolongations of myocardium or extensions of the fibrous valve rings are frequently present in the atrioventricular valves. Gross and Kugel[2] did not regard such extensions as part of the valves, and, when valve vascularization was confined to intravalvular prolongations of cardiac muscle or fibrous connective tissue extensions from the annulus, they did not regard the valve as being vascularized. So far as the relation of blood vessels to valvulitis is concerned, it must be admitted that it is the vessels beyond the basal third which are significant, since the most commonly occurring inflammatory lesions are in the distal rather than the proximal portions of valves. Since the difference in the anatomical concept of a valve applied chiefly to the atrioventricular leaflets, 104 atrioventricular leaflets from noninflammatory hearts in which vessels were limited to the proximal third were cut in such a manner that blocks for histological examination included the sites of vascularization. The results are shown in Table IV.

TABLE IV

LOCATION OF VESSELS IN ONE HUNDRED AND FOUR UNINFLAMED ATRIOVENTRICULAR LEAFLETS IN WHICH VASCULARIZATION WAS LIMITED TO THE BASAL THIRD OF THE LEAFLETS

	PERCENTILE INCIDENCE
Vessels in myocardial muscle wedge in leaflets	62
Vessels in extension of fibrous valve ring into leaflet	25
Vessels in atrial lamella of leaflet	10
Vessels in ventricular lamella of leaflet	3

Table IV reveals that only 13 per cent of the atrioventricular valves reported by us as being vascularized in their proximal portions would be accepted by Gross and Kugel[2] as being truly vascularized valves.

Since all valves in injected hearts were drawn to scale on square millimeter paper with the location and length of vessels indicated, it is possible to determine the extent to which each valve was vascularized. All vascularized valves were classified in two groups, according to whether the vessels were confined to or extended beyond the proximal or basal third of the leaflet or cusp. These data are recorded in Table V.

TABLE V

	UNINFLAMED HEARTS		INFLAMED HEARTS	
	VESSELS LIMITED TO PROX. THIRD (PERCENTILE INCIDENCE)	VESSELS EXTENDING BEYOND PROX. THIRD (PERCENTILE INCIDENCE)	VESSELS LIMITED TO PROX. THIRD (PERCENTILE INCIDENCE)	VESSELS EXTENDING BEYOND PROX. THIRD (PERCENTILE INCIDENCE)
Aortic	2	3	7	20
Pulmonic	10	4	23	14
Mitral	26	24	22	66
Tricuspid	21	10	23	28

With the elimination of all valves vascularized only in their proximal portions, there still remain 32 per cent of all noninflammatory and 69 per cent of all inflammatory hearts with one or more valves vascularized beyond the proximal third of leaflets or cusps.

There is considerable difference in the mean age of the two groups of individuals from whom inflamed and uninflamed hearts were obtained. The mean age of the inflammatory group was fifty years and of the noninflammatory group, thirty-four years. It was desirable to reclassify the noninflammatory group according to age in order to determine if any age relationship to extent of vascularization exists. Table VI shows the observed relation of age to occurrence and extent of valve vascularization in uninflamed hearts.

TABLE VI

THE INCIDENCE AND EXTENT OF VESSELS IN UNINFLAMED VALVES IN RELATION TO AGE

AGE IN YEARS	NO. OF CASES	PER CENT OF HEARTS IN WHICH VESSELS EXTENDED BEYOND PROXIMAL THIRD OF VALVE	TOTAL PERCENTAGE OF HEARTS IN WHICH ONE OR MORE VALVES WERE VASCULARIZED
0-20	77	19.5	54.5
21-40	61	26.0	59.0
41-60	86	37.0	76.5
61-80	31	61.0	77.0

The two significant changes in valve vascularization in relation to age are seen. The first is the absolute increase of valve vascularization, from an incidence of 54.5 per cent in the first two decades to an in-

cidence of 77 per cent in the two decades between sixty-one and eighty years. The second is the relative increase in the extent to which valves are vascularized, beginning with a 19.5 per cent incidence in the youngest age group and increasing to 61 per cent in the oldest group, in which one or more valves were vascularized beyond the proximal third. This observation of the increasing incidence of valve vascularization with age is in accord with the earlier data of Wearn, Bromer, and Zschiesche. A rearrangement of their data is shown in Table VII.

TABLE VII

THE INCIDENCE OF VESSELS IN THE VALVES OF EIGHTY-THREE UNINFLAMED HEARTS IN RELATION TO AGE*

AGE PERIOD	NO. OF CASES	TOTAL PER CENT OF HEARTS IN WHICH ONE OR MORE VALVES WERE VASCULARIZED
0-20	13	60
12-40	19	74
41-60	36	90
61-80	15	100

*Wearn, Bromer, and Zschiesche.[1]

Their data also show an increasing incidence of vessels in valves with age and in the older age groups show a higher incidence of vascularization than that observed in the present study. The difference may be the result of chance variation in hearts examined or may be due to better injections obtained with India ink than were obtained with lamp black or soluble blue. (See Table I for comparison of various injection fluids.)

SUMMARY AND DISCUSSION

The coronary arteries of 333 hearts were injected with a suspension of lamp black or soluble blue, and the occurrence and distribution of vessels in the valves were studied. The hearts were divided into two groups according to whether there was evidence of inflammatory heart disease or not. Careful macroscopic and exhaustive microscopic examination was carried out for the purpose of establishing the noninflammatory group, which, so far as could be determined, included no instance of healed or active myocardial or endocardial inflammation.

In the noninflammatory group there were 255 hearts from individuals ranging from infancy to old age, the mean age being thirty-four years. Sixty-six per cent of these showed vascularization of one or more valves. Microscopic examination of the vascularized valves showed that, in a large proportion of the valves vascularized only in their proximal portion, the vessels were confined to prolongations, either of myocardial muscle fibers or of the fibrous valve ring beyond

the base and into the valve. In 32 per cent of the entire group one or more valves were vascularized beyond the proximal third of the leaflets or cusps.

Both the occurrence and the length of vessels in valves of noninflammatory hearts increased with age. There appears to be an acquisition of new vessels in valves with advancing age and also an age increase in the extent to which individual valves are vascularized. The increased incidence of valves vascularized was not as striking as was the increased number and length of vessels in the valves vascularized.

The increased incidence and extent of vessels with age would suggest that the valves were the seat of occult active or unrecognized healed inflammation. Unrecognized inflammation, however, does not suffice to explain the existence of all vessels in valves in view of the fact that in 19 per cent of the normal hearts of children under ten years of age, one or more valves were vascularized beyond their proximal third. Furthermore, there were forty-nine infants under one year of age in the noninflammatory group and in twelve of them one or more of the heart valves were vascularized beyond the proximal third. It seems probable then that normal valves are commonly vascularized beyond their proximal third and that, if the acquisition of new vessels and the lengthening of old vessels in valves with advancing age are due to inflammation, the inflammation must leave no recognizable trace of its occurrence.

A similar study was made of the incidence and character of valve vascularization in seventy-eight hearts recognized as being or as having been the seat of inflammation. Eighty-eight per cent of the entire group showed vascularization of one or more valves, and in 69 per cent of the entire group one or more valves were vascularized beyond their proximal third. These figures indicate a considerable increase in the occurrence and extent of valve vascularization in this group as compared with the noninflammatory group. The actual difference was not as great as the apparent difference because the mean age of the inflammatory group was fifty years, whereas that of the noninflammatory group was thirty-four years. A comparison of the incidence of vascularization in the inflammatory group with that in a comparable noninflammatory age group showed a total incidence of 88 per cent in the former as compared with 76.5 per cent in the latter and an incidence of vascularization beyond the proximal third of 69 per cent in the former as compared with 37 per cent in the latter.

The frequency with which the various individual valves were vascularized followed the same sequence in the inflammatory and in the noninflammatory groups, the mitral having the highest incidence in each group, followed by the tricuspid, pulmonic, and aortic in diminishing frequency. The sequence of the incidence with which

the various valves were vascularized in the inflammatory group did not correspond to the frequency with which the various valves were affected by inflammation. The mitral valve was most commonly the seat of valvulitis, followed by the aortic, tricuspid, and pulmonic valves in diminishing frequency.

The incidence of the vascularization of multiple valves in each heart was higher in the inflammatory than in the noninflammatory group. This is especially apparent in the case of vascularization of all four valves in a single heart. Seventeen per cent of the entire inflammatory group showed vessels in all four valves in contrast to an incidence of less than 1 per cent of similarly extensive vascularization in the noninflammatory group.

CONCLUSIONS

1. *Vascularization of Normal Valves.*—The frequent presence of blood vessels in the valves of infants and children in whom the absence of degenerative or proliferative age changes makes possible the recognition of normal anatomical structure definitely establishes the existence of vessels in normal heart valves.

2. *Inflammatory Vascularization of Valves.*—The increased incidence and extent of vascularization of valves which are the seat of inflammation indicate that valves not originally vascularized may acquire vessels incident to inflammation.

3. *Age Changes in the Occurrence and Character of Vascularization of Noninflammatory Valves.*—There is an apparent age increase in the incidence and extent of valve vascularization which may represent a normal anatomical age change or may be the result of occult active or healed valvulitis.

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CONCERNING A NEW CONCEPT OF THE GENESIS OF THE ELECTROCARDIOGRAM*

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THE problem of the genesis of the electrocardiogram has intrigued investigators ever since the time of Waller and Einthoven. The problem, which is to define and account for the electrical field created by the heart, can be divided into three phases: (1) the time sequence and spatial orientation within the heart of the electromotive forces set up; (2) the distribution of the electrical currents generated by the heart within the body as a whole; and (3) the influence on the distribution of the electrical currents which results from the variable electrical conductivity of the tissues in contact with the heart, i.e., those tissues which make the bridge between the generator and the conducting medium. While considerable attention has been paid to the first two aspects of the problem, little thought has been given to the last. During the past few years, we have been concerned in this laboratory more particularly with this last aspect, and our studies have led us to a new concept of the genesis of the electrocardiogram. In the present communication an attempt is made to present this concept and to summarize briefly the evidence which has led us to this view. The material will be presented under the three aspects outlined above with the aid of schematic diagrams. No attempt will be made to review the extensive literature or to become involved in controversies with views already expressed since presentations of these controversial views are available in the literature, viz., Lewis,[1] Craib,[2] Katz,[3] Wilson and his coworkers,[4] Groedel,[5] Eyster and his collaborators,[6] and Gilson and Bishop.[7]

THE TIME SEQUENCE AND SPATIAL ORIENTATION WITHIN THE HEART OF THE ELECTROMOTIVE FORCES SET UP

The active heart in situ can be considered as equivalent to a composite electric battery placed in a relatively large volume of a conducting medium, a battery which varies the orientation of its poles and its potentials during the cardiac cycle. There is now a large body

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of evidence to show that resting muscle cells, including the heart, are in a state of electrical polarization at their surfaces. There is still some controversy concerning the manner in which this polarized state is brought about, but it has been shown to depend on the activity of the living cell, which requires energy for its creation and maintenance. Any attempt to destroy this state of electrical polarization tends to bring about its restitution unless the cell is killed. It has also been established that stimulation and the process of activity cause a temporary loss of the polarized state of the cell (depolarization). Sometimes, as in an injured region of the heart, there is a balance between the processes of depolarization and restitution, resulting in a sustained state of partial or almost complete depolarization. Advantage has been taken of this last fact to define the electrical activity of the various fractions of the heart during the cardiac cycle. For example we (Jochim, Katz and Mayne[8]; Katz, Jochim, and Abramson[9]) have determined the synchrony of the onset of depolarization and of the reestablishment of the polarized state in various fractions of the mammalian heart. This was made possible by connecting in turn various spots of the heart through an Einthoven recording string galvanometer with a spot rendered inactive by injury (Jochim, Katz, and Mayme[8]). Evidence was presented, which has recently been confirmed by H. Wiggers,[10] that the curves so recorded can be used to measure the time course of events beneath the uninjured spots. It was found by reference to a simultaneously recorded lead (Lead II) that both the time of onset of depolarization and the time of the reestablishment of the polarized state were not synchronous in all the spots. Further, the time span between these two events showed a variation of as much as 0.03 sec. in the different spots, and the time curves from the various spots were out of phase.

In Fig. 1 an attempt is made to show these facts schematically. In this figure three uninjured spots of the dog's heart are depicted, connected in turn through a recording Einthoven string galvanometer with an injured spot. In the frame are shown the time curves which might have been obtained in this way during a heart cycle. The two vertical lines running between the curves represent, respectively, the peak of the major phase of the QRS complex and the peak of the T-wave in a simultaneously recorded Lead II. The curves show that both depolarization and repolarization are out of phase in the three spots. Depolarization starts after the peak of QRS_2 in the top curve, is simultaneous with the peak of QRS_2 in the middle curve, and starts before the peak of QRS_2 in the bottom curve. The order of reestablishment of the repolarized state is the exact reverse; viz., it occurs before the peak of T_2 in the top curve, is simultaneous with this point in the middle curve, and occurs after the peak of T_2 in the bottom

curve. The duration of time between depolarization and repolarization is, therefore, unequal, the time span being shortest in the top and longest in the bottom curve.

It is this asynchrony of similar events in different fractions of the heart that gives rise to the electromotive forces which cause electrical currents to flow within the heart and from the heart throughout the body. This, therefore, is the cause of the electrical field which we tap when electrocardiograms are recorded. A survey of the evidence in the literature available in 1928, with which more recent work has fitted, led the author[3] at that time to enunciate the process of genesis in the following terms:

"If we consider the heart a syncytium—and in the present state of our knowledge this view is just as reasonable as the alternative view that the heart is composed of individual discrete cells—then it follows

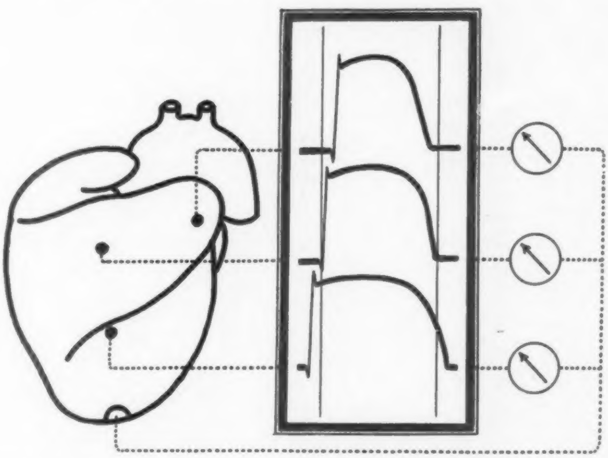

Fig. 1.—This is a diagram showing in the frame the curves which could be obtained from the three spots (solid circles) on the heart if they were connected in turn through galvanometers to an injured area (open circle). The two vertical lines running through the curves represent the peak of QRS of Lead II simultaneously recorded. The asynchrony of the three curves is clearly shown as well as the difference in their time spans. Discussed in text.

that as soon as a region becomes active it will tap the inside of the rest of the heart's syncytium. The active region will therefore act as the negative pole, and the rest of the heart, which is inactive, will of necessity act as the positive pole, the source and sink of the electrical potential being ultimately referable to the two sides of the intact membrane or surface. . . . Certain regions gain an advantage because the intensity of current flow varies not only with the difference in potential, but also with the amount of electrical resistance between regions having such differences of potential. Obviously, the greatest intensity of current flow will be between adjacent active and inactive regions, as the resistance is least here. For this reason adjacent active and inactive regions will appear to act as the two poles of the source

of the bioelectric current, although in reality it is the two sides of the intact surface layer or membrane in the inactive regions which is the source.''

The exact geographical pattern of the asynchrony of depolarization and repolarization is at present undetermined. The classical picture presented by Lewis and Rothschild[11] has been questioned recently by Robb,[12] H. Wiggers,[10] and Abramson and Jochim.[13]

Aside from this source of electrical current, which may be briefly stated as the asynchronous depolarization and repolarization in the various regions of the heart, two other possibilities for the generation of electrical currents must be considered. The first is the electromo-

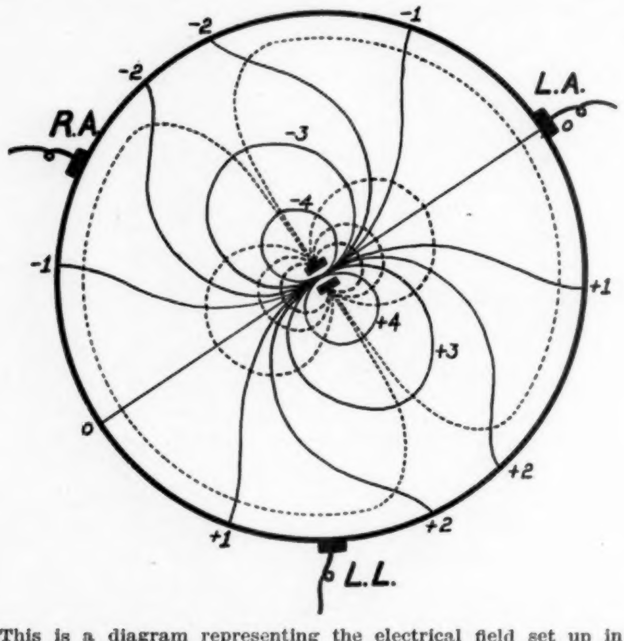

Fig. 2.—This is a diagram representing the electrical field set up in a circular homogeneous medium by a simple bipole placed in the center, indicated by the solid rectangles in the center. The solid lines indicate the lines of equipotential, the broken lines, the flow lines. The figures on the solid lines give the values of the potential lines in arbitrary units. *RA*, *LA*, and *LL* represent three electrodes placed at the angles of a triangle and are equivalent to the right arm, left arm and left leg electrodes. The triangle in this figure is equilateral. Discussed in text.

tive forces set up by the difference in the rate of migration of the positively and negatively charged ions when depolarization occurs (cf. Katz[3]). The second is frictional electricity. In recent work (Katz, Sigman, Gutman, and Ocko[14]) evidence was elicited that frictional electricity can set up electromotive forces when mercury in contact with the lungs is rhythmically agitated; such forces were demonstrated to occur in living unoperated dogs following the intravenous injection of mercury (Buchbinder and Katz[15]). The exact rôle played by these latter two factors is still unknown, but in all likelihood they are of minor significance.

DISTRIBUTION OF ELECTRICAL CURRENTS GENERATED BY THE HEART WITHIN THE BODY AS A WHOLE

The distribution of the currents from the heart within the body depends on the electrical properties of the various tissues composing the body. This phase of the problem can best be developed by means of simple models. In this laboratory we (Jochim and Katz[16]) have used such models. If a large circular dish containing concentrated salt solution is used and two electrodes are immersed in the center of the dish and connected to a 60 cycle 110 volt alternating current, then an electrical field is set up. This can be defined by using exploring

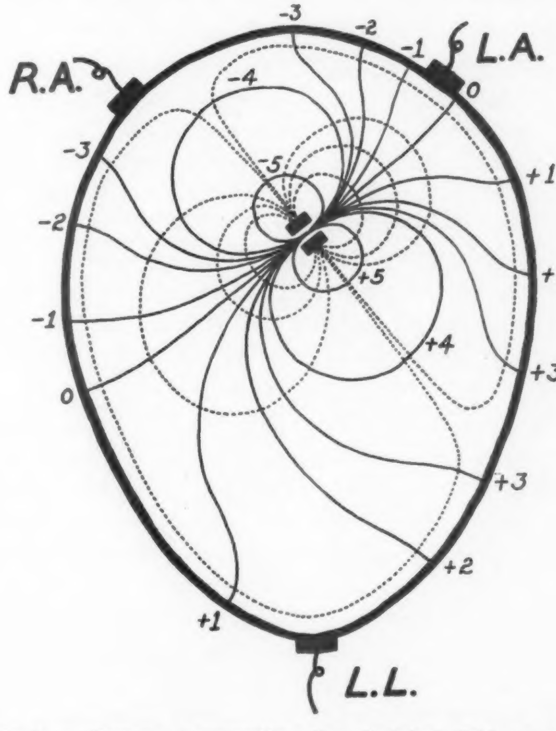

Fig. 3.—This is a diagram representing the electrical field set up in an ovoid homogeneous medium by a simple bipole placed eccentrically. Conventions as in previous figure. Note that the triangle at whose angles the electrodes *RA*, *LA*, and *LL* are placed is not equilateral. Discussed in text.

electrodes and a suitable method of measurement. (The method we used was suggested to us by Dr. A. Kolin of this department.) In this way the lines of equal potential in the field can be mapped out, and the lines of the current flow can be constructed as orthogonal trajectories. These lines will depict the distribution of the electrical flow and give information regarding the intensity of the flow of current and the gradient of the potential drop in the various parts of the field. The concentration of the lines of equipotential will give the potential drop, and the concentration of the lines of flow will give the intensity of the current flow.

The result of such an exploration is represented diagrammatically in Fig. 2; the lines of equipotential are shown as solid lines and the lines of current flow as interrupted ones. It will be seen that the current flow and the potential drop are greatest near the battery and least at the periphery of the field. If, in such a field, recording electrodes are placed at the periphery as indicated by *RA*, *LA* and *LL*, they form an equilateral triangle, and the Einthoven concept would apply accurately. In the body, however, these conditions are not fulfilled for several reasons: (1) the conducting medium of the body is not homogeneous nor is it spherical or circular; (2) the battery (the heart) is not centrally placed; and (3) the battery poles are of complex form. Let us consider the effect of each of these factors separately.

The electrical field of the body has the shape of the body; the limits are determined by the poor conducting environment surrounding it, viz., the outer layers of the integument and the air. The appendages, the head and the limbs, it has been established, have so little of the heart's current flowing in them and so small a gradient of potential drop (Wilson[17]) that they can be ignored without serious error. The shape of the electrical field can, therefore, be considered to be that of the torso. The heart, furthermore, is not in the center of this field but is sternad and considerably cephalad from the center. Obviously, both the shape of the conducting medium and the location of the battery in it will alter the electrical field.

In Fig. 3 is shown diagrammatically the electrical field that is obtained in an ovoid, homogeneous medium having the battery displaced upward from the center. The three electrodes, *RA*, *LA*, and *LL*, no longer form an equilateral triangle. This fact has been ignored or dismissed as of no significance, we believe unjustly, by many workers in the field. In fact, diagrams in many texts, of which Fig. 4 is an example, show at once how the positions of the three electrodes have been displaced to make the triangle appear equilateral. To accomplish this the body is foreshortened, the heart is put too far caudad, the leg electrode contact is displaced upward and to the right, and the arm electrode contacts are displaced laterally. It is not surprising that the Einthoven equilateral triangle concept has been questioned recently as to its practical utility (Zeisler,[18] Zeisler and Katz,[19] Eyster and his coworkers,[6] Koch-Momm,[20] and Storti[21]). Experience has convinced the author that the significance of axis deviation is not arrived at from the Einthoven equilateral triangle concept but rather on an empirical basis. Marked left axis deviation has been found, for example, in brown atrophy (Katz, Saphir and Strauss[22]), in displacement of the heart to the right with rotation (Robinow[23]) and, in accord with previous workers, we have found that the direction of the electrical deviation in the dog and in man does not always parallel the direction of the anatomical axis shift (Katz and Ackerman[24] and Katz and Robinow[25]).

The body is not a homogeneous conducting medium. Eyster and his collaborators[6] have shown clearly that the blood-filled compact muscle masses are sufficiently better electrical conductors than the other tissues of the body so that the electrical field of the body approaches that of a plane of homogeneous material, the greater dimensions of which are parallel to the plane formed by the standard limb electrodes. It can be shown that the introduction into a homogeneous conducting medium of conductors better and worse than the general medium will alter the electrical field set up by a battery in the medium. The amount of alteration will depend on several factors:

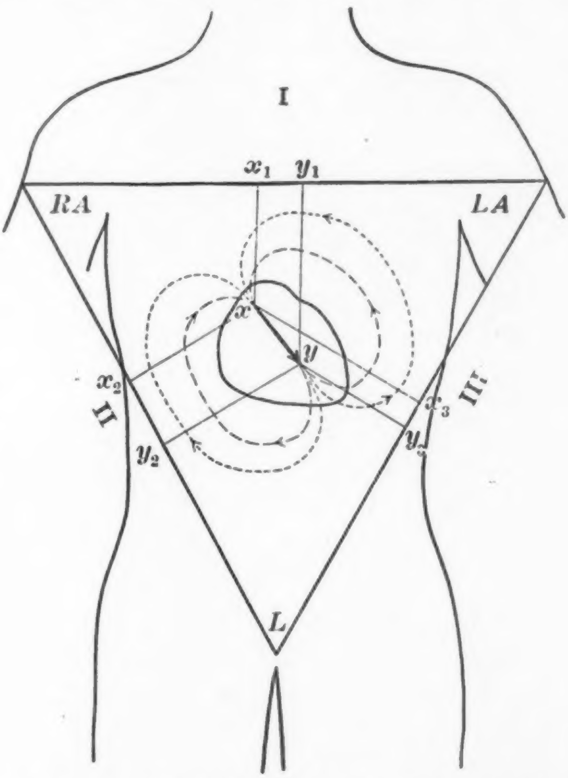

Fig. 4.—This is a reproduction of Fig. 96 from Wiggers' *Circulation in Health and Disease* (Lea & Febiger, ed. 2), which is modified from Fig. 1 of Pardee's *Clinical Aspects of the Electrocardiogram* (Hoeber). Discussed in text.

(1) the total volume of the nonhomogeneous conductors introduced, (2) the size of the individual masses of the introduced conductor, (3) the disparity between the specific electrical conductivity of the introduced mass and that of the surrounding medium, and (4) the distance of the introduced masses from the source generating the currents. The effect on the electrical field will be greater as the total volume introduced is increased, as the size of the individual masses is increased, as the disparity between the specific electrical conductivity of the introduced mass and the rest of the conducting medium is in-

creased, and as the introduced mass is brought toward the current source. If an introduced conductor is not spherical in shape, the effect will also vary, depending on how it is placed. When the introduced mass is a better conductor than the environment, it will push apart the lines of equipotential so that they are concentrated on its borders, and it will concentrate the lines of current flow within it. On the other hand, when the introduced mass is a poorer electrical conductor, the reverse will be true; it will concentrate the lines of equipotential within it; and it will spread the lines of current flow so that they are concentrated on its borders.

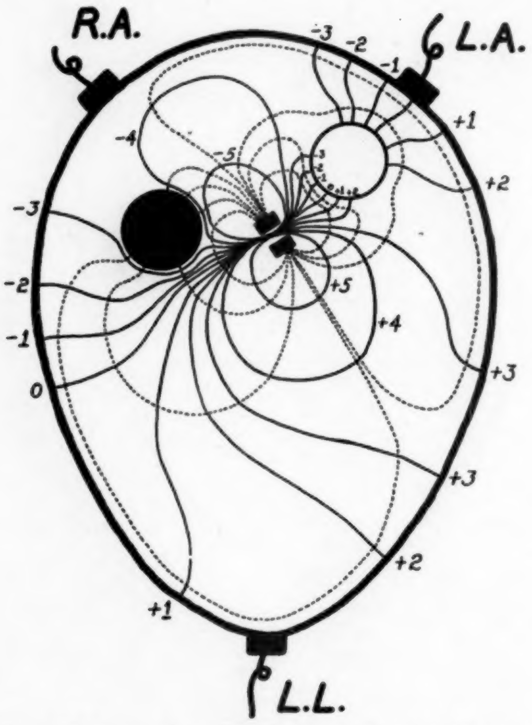

Fig. 5.—This is a diagram representing the electrical field set up in an ovoid nonhomogeneous medium by a bipole placed eccentrically. Conventions as in Fig. 2. Open circle represents a poorer conductor, and the solid circle a better conductor than the rest of the medium. Discussed in text.

In Fig. 5 is shown diagrammatically an example of the alterations in the electrical field which were caused by introducing a poor electrical conductor, like glass (open circle), and a good electrical conductor, like tin (solid circle), in the ovoid homogeneous medium shown in Fig. 3. The presence of such dissimilar conductors, even in a circular field such as shown in Fig. 2, might in itself be sufficient to prevent the accurate application of the Einthoven equilateral triangle concept.

Finally, the source of electricity in the heart is not a simple bipole but a battery with poles of complicated design, a design that changes rapidly

during the heart cycle, especially when the QRS complex is inscribed. The changes in design are a combination of the following: (1) the location and angle of the bipole within the heart, (2) the distance between the two poles, (3) the area of each pole, (4) the angle at which the two poles are placed in relation to each other, and (5) the three-dimensional shape of each pole. In actuality, the shape of each pole is complicated, and it does not lie in one plane. It is because of these factors that Eyster and his coworkers[6] found that when the

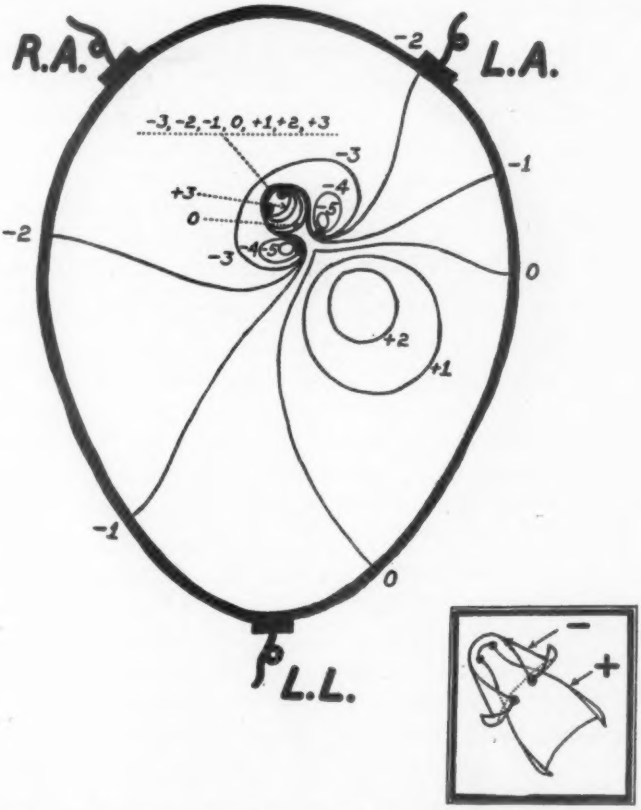

Fig. 6.—This is a diagram representing the electrical field set up in an ovoid homogeneous medium by a bipole of complex design placed eccentrically. The shape of the bipole as viewed from above is shown in the frame below. Also indicated are the points where it cuts the plane of the field mapped out. Conventions as in Fig. 2. The flow lines have been omitted as they are so complicated that they would confuse the illustration. Discussed in text.

heart is placed in a uniform conducting field, the resultant electrical field is better fitted by two independent small bipoles than by one. Actually, however, the battery consists of two poles, a positive and a negative one, of very complex design, and it does not lend itself readily to reduction to simple theoretical bipoles.

In Fig. 6 is shown diagrammatically an example of the alterations in the electrical field which were caused by substituting a bipole of

complicated design for the simple one used in Fig. 3. The marked alteration in the field is readily seen by comparing the two figures.

All of these facts have been known to the majority of workers who have delved deeply into the subject of the electrical field, but there has been a tendency to minimize the significance of the variables we have outlined above with the result that the Einthoven equilateral triangle concept has been accepted by most electrocardiographers as axiomatic or, at least, as a good approximation to an accurate presentation of the conditions. It is the experience of the author that except in the hands of a few who recognize, as did Einthoven himself, the limits of his concept, the concept has confused rather than clarified our understanding of the electrical field. A return to the more general view as outlined in this section should serve to clarify the problem.

THE INFLUENCE ON THE DISTRIBUTION OF THE ELECTRICAL CURRENTS WHICH RESULTS FROM THE VARIABLE ELECTRICAL CONDUCTIVITY OF THE TISSUES IMMEDIATELY IN CONTACT WITH THE HEART

A further factor complicating the general problem outlined in the preceding sections defining the genesis of the heart's electrical currents and the properties of the conducting medium of the body is the important part played by the electrical conductivity of the tissues which serve as the bridges between the heart and the body. Recent work in this laboratory has shown that these bridges in contact with the heart are not uniform in their ability to conduct away the currents which the heart generates. Not all regions of the heart are in contact with good electrical conductors, and some regions are in contact with poor electrical conductors. It is obvious that those that are in contact with good conductors have a decided advantage over other regions of the heart in their influence on the electrical field. The evidence for this viewpoint is summarized below.

We have found that the electrocardiographic contour of experimentally induced premature contractions from fixed points of the heart can be readily altered by shifting the position of the heart (Katz and Ackerman[24]) or by introducing a metal shunt between a region of the heart and some part of the body (Abramson and Katz[26]). We have found also that the electrocardiographic contour of a fixed type of intraventricular block can be altered by a shift in the position of the heart both in the experimental animal (Ackerman and Katz[27]) and in man (Kissin, Ackerman and Katz[28]). It can also be altered in the animal by introducing a metal shunt between a region of the heart and some part of the body (Abramson and Katz[26]). An assay of the electrocardiographic contour of various types of intraventricular block in man has shown further that the contour does not always coincide with the functional evidence of block in the right and left

ventricle (Katz, Landt, and Bohning[29]). The electrocardiographic evidence of myocardial infarct location obtained in man from the standard three leads does not always fit with the location established post mortem (Saphir, Priest, Hamburger, and Katz[30]). Injury with alcohol within a large region of the dog's heart does not give a constant type of electrocardiographic deformity (Korey and Katz[31]). All these facts suggested that the location of defects in the conduction system, of ectopic pacemakers, and of injured regions within the ventricles is only one of the factors which determine their electrocardiographic contour. Another factor which appears to be important is the position and shape of the heart.

Another line of evidence which we have recently uncovered points to the same deduction. We found that surrounding the ventricles by insulating material (a glass oncometer) greatly decreased the magnitude of the ventricular complex in the standard three electrocardiographic leads. Analysis showed that such insulation tends to confine the currents generated to the heart. The introduction of insulators (rubber sheeting) between the heart and various parts of the surrounding structures had an unequal effect, depending on where the insulator was placed (Katz and Korey[32]). The results are summarized in Table I taken from this report. This disparity in action was taken as evidence indicating disparity in the electrical conductivity of the various structures adjacent to the heart. The lungs and the large systemic and pulmonary vessels coming off from the heart were found, in this way, to be poor conductors, while the muscular structures of the chest wall, especially the diaphragm and posterior paravertebral muscle mass, were found to be good conductors.

Experiments of a converse nature were done with good conductors. Thus, when the heart was surrounded by a metallic conductor, a decrease in the electrocardiogram in the standard three leads was obtained (Katz, Sigman, Gutman and Ocko[14]). This result is attributed to the fact that the good conductor shunts back the currents generated and so tends to prevent the currents from passing to the rest of the body. The effect of insulators and excellent conductors in electrical fields is well known to physicists. Alterations in the contour of the standard three-lead electrocardiograms were also obtained by a similar shunting action when warm isotonic saline was placed in the dog's chest.[14]

Furthermore, evidence was secured that the introduction of good electrical conductors adjacent to the heart altered the electrical records obtained when leading directly from the heart or when the leads were a combination of one electrode on the heart and another at a distance from it.[14] The action of these introduced conductors was shown to depend on (a) their offering a by-pass for the currents generated by the heart, thereby decreasing the amount passing

through the galvanometer circuit, (b) their altering the path taken by currents to distant points, and (c) their altering the relative contribution of the various regions of the heart to the recorded electrical curves. These experiments with introduced good electrical conductors show how the electrocardiogram can be modified by altering the contacts with the body and support the general concept that the natural contacts play an important rôle.

TABLE I
(TAKEN FROM KATZ & KOREY[32])

THE EFFECT OF INSULATING THE HEART ON THE SUM OF THE MAJOR DEFLECTIONS OF QRS IN THE THREE STANDARD LEADS

DOG NUMBER	(A) MASSIVE INSULATION OF HEART EXCEPT FOR SYSTEMIC AND PULMONARY VESSELS	(B) INSULATION OF HEART FROM ANTERIOR CHEST WALL	(C) INSULATION OF HEART FROM POSTERIOR CHEST WALL	(D) INSULATION OF HEART FROM DIAPHRAGM	(E) INSULATION OF HEART FROM RIGHT LATERAL CHEST WALL	(F) INSULATION OF HEART FROM LEFT LATERAL CHEST WALL	(G) INSULATION OF LUNGS FROM HEART AND ENTIRE CHEST WALL EXCEPT FOR PULMONARY VESSELS BETWEEN FORMER TWO	(H) INSULATION OF HEART FROM SYSTEMIC VESSELS
Dog on back								
1	++++		++++					±
2	++++	±	+++	++				
3	++++		+++	++			±	±
4			++++				±	±
5	++++	±	+++	±			±	
6	++++		++++	±			+	±
7	+++	±	++	±			±	
8	++++		+++				±	
Dog on abdomen								
9	++++	+++	±					
10	+++	++	±	±				
Dog on left side								
11	+++	±	±	++		++		
12	++++	±	±	+		++		
Dog on right side								
13	++++	±	+++	++	±			
14	+++	±	+++	+++	±			

± is equivalent to decrease of from 0 to 15 per cent.
+ is equivalent to decrease of from 15 to 25 per cent.
++ is equivalent to decrease of from 25 to 50 per cent.
+++ is equivalent to decrease of from 50 to 75 per cent.
++++ is equivalent to decrease of from 75 to 100 per cent.
NOTE: The sums of these percentages, because of the roughness of the approximation, of course do not give 100 per cent.

Evidence of a similar sort was obtained in another way. Katz, Gutman, and Ocko[33] demonstrated that certain regions of the heart may gain a decided advantage over the rest merely because they are in contact with a good electrical conductor, provided they are nearer to one of the recording electrodes. This was shown by connecting various regions of the heart with various parts of the body by means of a good electrical nonpolarizable shunt. The region of the heart so

shunted sets up its own electrical field, which summates with that set up by the heart through its natural contacts. The alterations obtained were of two sorts (or intermediate or mixed forms): (a) diphasic additions when the region in the heart under the shunt electrode was not injured and (b) monophasic additions when the region under the shunt electrode was injured. The direction and magnitude of the electrical addition were found to depend on the resistance of the shunt circuit and the distance between the point of the shunt on the body and the recording electrodes. The two types of additions are diagrammatically represented in Fig. 7, where the two directions they may take are shown by curves *A* and *B* and the variation in magnitude by the arbitrary scales at the left.

Following up the view that there is an electrical field, we have explored, recently, the lines of equipotential inscribed on the surface

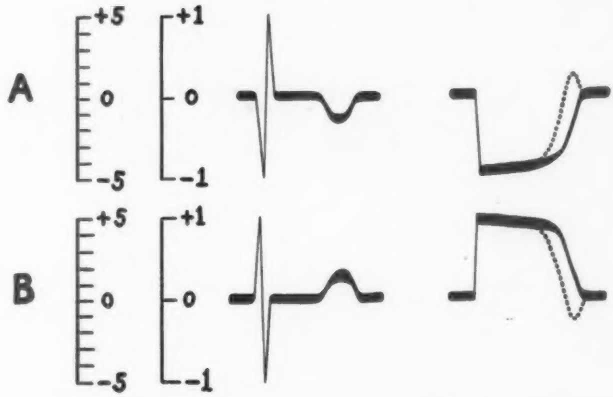

Fig. 7.—This is a diagram (previously published[33]) showing two types of additions which can be obtained when a region of the heart is shunted to the body by a good electrical conductor. On the left are the diphasic, and on the right are the monophasic types of additions. *A* and *B* represent the two directions these additions may take. The arbitrary scales on the left represent the various magnitudes the additions may take. Discussed in text.

of the body (Robinow, Katz, and Bohning[34]). We have so far, because of its relative simplicity, confined ourselves to the part of the heart cycle during which the T-wave is inscribed. The potential of the peak of the T-wave at various points on the body was noted, the potential being determined as a relative value compared to that of the leg. While the potential at the leg is not zero and the peak of the T-wave is not homologous in the various spots, the errors introduced in these ways are of no real significance for the use we made of the data. We found that the lines of equipotential were more concentrated over the precordium than elsewhere and were irregular in shape. We have paid particular attention to the line having a potential equal to that in the leg; that is, the places on the body on which no T-wave appeared when they were connected through a galvanometer

to the leg. This line we have called the line of "leg potential." This line was found to vary in its position under different clinical conditions. In Fig. 8, for example, is shown the complicated course taken by the line of "leg potential" during the peak of the T-wave in a fifty-year-old subject with congenital heart disease. It is difficult to see how the simple concept of the Einthoven triangle could explain the results obtained, whereas it fits into the electrical field concept deduced from our work.

The importance of good electrical contact in giving particular regions of the heart an advantage was shown by a different type of experiment (Katz, Gutman, and Ocko[33]). Figure 9 illustrates the results. In this dog the heart had been separated from the posterior paravertebral muscle mass so as to permit the application of a boot

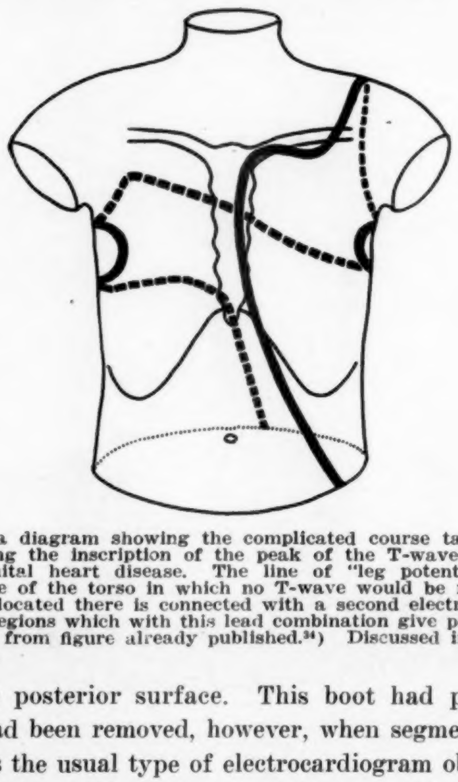

Fig. 8.—This is a diagram showing the complicated course taken by the line of "leg potential" during the inscription of the peak of the T-wave in a fifty-year-old subject with congenital heart disease. The line of "leg potential" represents the points on the surface of the torso in which no T-wave would be registered when the precordial electrode located there is connected with a second electrode on the left leg. This line separates regions which with this lead combination give positive and negative T-waves. (Modified from figure already published.[34]) Discussed in text.

electrode on the posterior surface. This boot had produced injury beneath it. It had been removed, however, when segment *A* was taken. Segment *A* shows the usual type of electrocardiogram obtained with the heart in this position. When, however, the heart was placed back in contact with the posterior paravertebral muscle mass (segment *B*), a marked monophasic addition was obtained in Leads II and III. This monophasic addition disappeared when the heart was returned to its preexisting position (segment *C*). It is obvious that the injury had persisted after the boot was removed but did not affect the electrocardiogram because it was not advantageously situated. By placing this

injured area in contact with a good electrical conductor, the posterior paravertebral muscle mass, it gained sufficient advantage to dominate the curve. The change in contact of the heart in its two positions is illustrated diagrammatically in Fig. 10. This experiment shows that regions of the heart at a disadvantage in contributing to the electrical field can gain a definite advantage by being brought in contact with a good conductor. It demonstrates graphically what is accomplished when precordial leads are employed. Here, however, instead of mov-

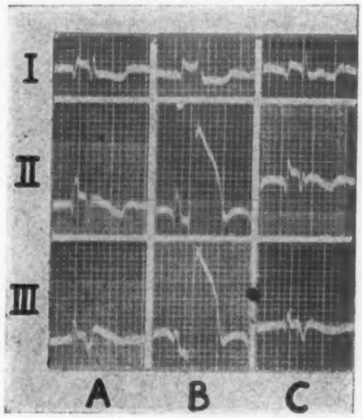

Fig. 9.—Series of electrocardiograms showing the importance of good electrical contact of an injured area of the heart in bringing out the characteristic contour. The injured area in this open-chested anesthetized dog was located posteriorly on the ventricles. Segments *A* and *C* show the standard three leads when the apex of the heart was moved up and the heart separated from the posterior paravertebral muscles. Segment *B* shows the standard three leads when the heart was brought in contact with this muscle mass. (Previously published.[33]) Discussed in text.

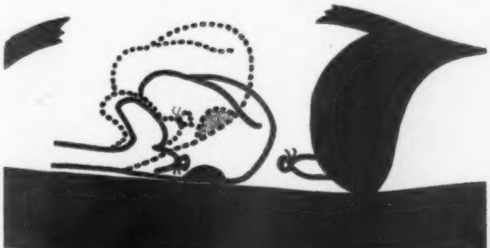

Fig. 10.—This is a diagram of a sagittal section of the open-chested dog showing the two positions of the heart from which the records in Fig. 9 were obtained; dotted heart outline when segments *A* and *C* were recorded, solid heart outline when segment *B* was recorded. The injured area is shaded. The good electrical conductors are shown on the heart as shaded areas. Discussed in text.

ing the heart, the recording electrode is brought closer to the "silent" areas. It is a case of "Mohammed going to the mountain" instead of the "mountain going to Mohammed."

In view of the evidence presented above, it is apparent that changes in the electrocardiogram can result from variations in the relative position of the electrical conductors in contact with the heart. This

may be caused either by alterations in the position or shape of the conductors or by changes in the position or shape of the heart itself. As a result, regions of the heart which normally exert a great influence on the electrocardiogram may become "silent," while other regions previously "silent" may now exert a prominent effect.

Such changes in the contacts between heart and body occur during the heart cycle. It follows that the regions of the heart which play the dominant rôle in giving rise to the T-wave may be different from those giving rise to the QRS complex.

Such changes in the contacts between heart and body occur also during respiration and thus account for the variations in the electrocardiographic contour seen during the respiratory cycle. Displacements of the heart alter the contacts between heart and body, as do hypertrophy and dilatation of the various heart chambers. The electrical evidence of axis deviation and preponderant hypertrophy may thus turn out to be the result of these changes in contact rather than

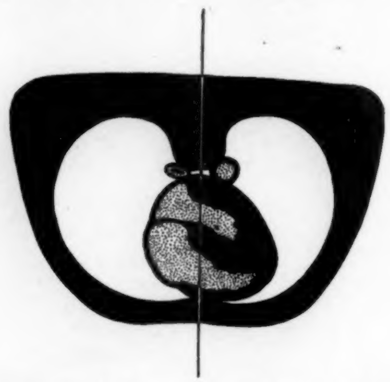

Fig. 11.—This is a diagram of a cross-section of the human body at about the level of the middle of the ventricles to represent the location of the various types of electrical conductors in contact with the heart which serve to bridge the gap between heart and body. The good electrical conductors are shaded, and the poorer ones are left blank. The blood-filled cardiac cavities are stippled. The vertical line shows the plane in which Fig. 12 was drawn. Discussed in text.

of some hypothetical resultant vector dependent on the spread of the impulse within the heart. The occurrence clinically of tremendous axis deviation in the absence of intraventricular conduction disturbances would lead to the inference that the axis deviation in intraventricular block might be due, in part at least, to a similar cause. It is, therefore, unjustifiable to ascribe the entire disturbance to alteration in the spread of the impulse, and ignore the influence which position and shape changes in the heart have in modifying the contacts between the heart and the body. A similar argument holds also in localizing regions of infarction. In other words, account must be taken not only of the intrinsic changes within the heart, but also of the contacts between the heart and the body. Our results, given above, point clearly to this conclusion.

Edema in the tissues surrounding the heart, and solid tumor masses.

by altering the electrical nature of the contacts between heart and body can modify the electrocardiogram. Infarcts of the lung, when adjacent to the pericardium, should also have a similar effect. Evidence of this sort, however, is still incomplete, and further work along these lines is indicated.

To recapitulate, our results indicate that the electrocardiogram is not a summation of events occurring in all parts of the heart but is primarily a summation of events occurring in those regions which are in contact with the better electrical conductors. Other regions play a relatively lesser rôle.

From the evidence elucidated, we have attempted in Figs. 11 and 12 to indicate the relations of the better and poorer conductors in

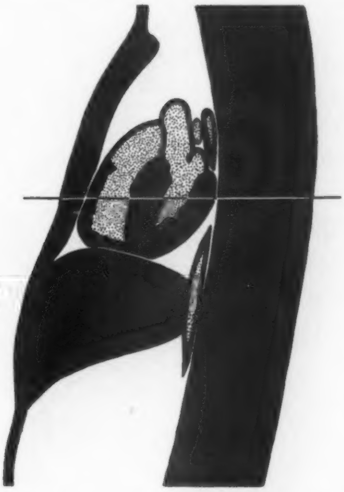

Fig. 12.—This is a diagram of a sagittal section of the human body to represent the location of the various types of electrical conductors in contact with the heart which serve to bridge the gap between the heart and body. Conventions as in Fig. 11. The horizontal line shows the plane in which Fig. 11 was drawn. Discussed in text.

contact with the heart of man. Figure 11 is a diagram of a cross section of the human body at about the level of the middle of the ventricles, and Fig. 12 is a diagram of a sagittal section of the human body. The heart muscle, the liver, and the chest walls are shown as solid black areas to indicate that they are good electrical conductors. The blood-filled cavities of the heart are stippled, and the lungs and alveolar mediastinal spaces are left blank to indicate that they are poor electrical conductors. According to the experiments with models outlined above, the electric currents will flow primarily through the solid areas. The flow lines will be most concentrated anteriorly where the good conductors are thinner than elsewhere in the chest; this will also be true of the lines of equipotential.* The potential

*The reason for this is that when dealing with equally good conductors in parallel separated by a poorer conductor, the thinner one will have the more concentrated current flow.

gradient in this region will also be steepest. In the lungs the current flow will be the least and the potential gradient the most gradual. The conditions as to current flow and potential gradient will be intermediate posteriorly and caudad.

According to the concept presented, the regions of the heart which will have the greatest effect on the distant electrical field and hence on the electrocardiogram will be those in contact with the diaphragm (the caudad regions of right auricle, right ventricle and left ventricle) and those in contact with the posterior paravertebral muscle mass (the base of left ventricle and the posterior aspect of left auricle). The anterior surfaces of the right auricle, right ventricle and left ventricle in contact with the anterior chest wall over the precordium will have a less important influence, while the rest of the heart shielded from the body by the lungs will have an unimportant influence, especially in the upper lateral parts of the heart where the lung is so thick that, practically, it completely shields these parts of the heart from the chest walls. The difference obtained in the experiments of Katz and Korey[32] between the electrical conductivity of the lungs and that of the muscles is so marked—being of the order of 1 to 10 in the open-chested animal—that the differences outlined above cannot be dismissed as of little actual significance. This great difference in conductivity, we believe, is primarily responsible for the "silent" regions of the heart.

SUMMARY

The electrocardiogram as shown by the evidence presented above, is a record of events in favored rather than in all regions of the heart. It registers the play of electromotive forces set up from moment to moment in these favored spots rather than the balance of the electromotive forces set up in the entire heart. It gives the order of invasion and retreat in these favored regions and depicts disturbances in these processes, primarily as they affect these favored regions. Similarly, it reveals injury currents affecting these particular regions but misses injury currents in other regions not so favorably situated. The precordial leads are from this viewpoint a method of bringing out into the open lesions in regions of the heart which are not favorably situated for notice by the ordinary distant leads.

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HEART DISEASE IN CHILDREN*

A. Rheumatic Group

I. Certain Aspects of the Age at Onset and of Recurrences in 488 Cases of Juvenile Rheumatism Ushered in by Major Clinical Manifestations

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THIS report is based on a study of 488 rheumatic children. It deals with the clinical aspects of the *age at onset* and of *recurrences* in juvenile rheumatism. The children were selected exclusively on the basis *of major rheumatic affections† as the first manifestations of the disease.* This method of selection makes easy the identification of the disease and utilizes well-defined initial episodes as reliable points of reference in timing recurrent affections. The cases constitute a subgroup of 750 cases of rheumatic fever observed in the Children's Cardiac Clinic of Mount Sinai Hospital, of which the population followed in the course of fifteen years was 1,107. Since all these cases are intended to serve as material for future studies related more or less to the subject of this paper, the original group is classified and presented in Table I. It is divided into three parts: A, rheumatic group; B, congenital cardiacs; and C, cardiac suspects.

The rheumatic group consisting of 750 patients has been further subdivided (Table I). The members of subdivisions 1, 2, and 3 have in common a history of at least one acute major *rheumatic* episode.‡ Patients with a history of fleeting muscle or joint pains only, though heart disease was present, were not included.

*From the Children's Cardiac Clinic of the Mount Sinai Hospital and the Heart Committee of the New York Tuberculosis and Health Association.

This paper is Number X in the series "Statistical Studies Bearing on Problems in the Classification of Heart Diseases."

†The term "rheumatic affection" is employed instead of "rheumatic infection" not because of doubt as to the infectious nature of acute rheumatism but to indicate reference to clinical forms of the disease.

‡By major episodes are meant well-defined clinical forms of juvenile rheumatism such as acute polyarthritis, carditis, or chorea.

Cases of clinical *polyarthritis* are those which exhibit migrating joint pains requiring rest in bed. Ambulatory cases, with mild muscle and joint pains or "growing" pains, were not included in this group.

The diagnosis *carditis* was made preferably during stay in a hospital. It was made only when it was recognized as an acute clinical manifestation but was not assumed to be present at the time of discovery of chronic valvular disease, since the cardiac lesion may have developed insidiously.

To accept the diagnosis of *chorea* on history is not difficult since a description of this disease is generally unmistakable. Diagnosis without sufficient description is unreliable. Such cases were excluded.

Subdivision 4 we designate as *presumably rheumatic* because, though a definite major rheumatic episode was not traced, the presence of mitral stenosis is taken as evidence of rheumatic affection.

The designation *probably rheumatic* in subdivision 5, implies doubt. It is employed to indicate that a well-defined clinical form of juvenile rheumatism has not been traced. All cases in this subdivision exhibit well-defined cardiac valvular defects such as mitral insufficiency, aortic insufficiency, or both. We find it desirable to designate these cases as probably rheumatic in order to separate cases in which there is a clear rheumatic background from those in which it is merely inferred.

The data were gathered in several ways. 1. Patients who were in continuous attendance at the Children's Cardiac Clinic, or who had been transferred to our Adult Cardiac Clinic, afforded the most de-

TABLE I

CLASSIFICATION OF RECORDS

GROUPS	NUMBER	PER CENT	M. & J. PAINS* PRECEDING MAJOR MANIFESTATION	VALVULAR LESION PRECEDING MAJOR MANIFESTATION	NO RECORD OF AGE AT INITIAL MANIFESTATION	MAJOR MANIFESTATION, THE FIRST SIGN OF RHEUMATIC INFECTION, AND AGE AT ITS OCCURRENCE KNOWN
1. A—Rheumatic (C V D)	523	47.2	50	21	21	431
2. Class E and F	56	5.1	5	0	0	51
3. Class F	6	0.5	0	0	0	6
Total (1, 2, and 3)	585	52.8	55	21	21	488
4. Presumbly rheumatic	63	5.7				
Total (1, 2, 3, and 4)	648	58.5				
5. Probably rheumatic	102	9.2				
Total (1, 2, 3, 4, and 5)	750	67.7				
6. B—Congenital H. D.	79	7.1				
7. C—Cardiac suspects (Class E)	278	25.1				
Grand Total	1107	99.9				

Legend for rheumatic subgroups, 1, 2, 3, 4, 5.

1, History of one or more attacks of a major rheumatic manifestation; well-defined cardiac valvular defects.

2, History of one or more attacks of a major rheumatic manifestation; physical signs abnormal, but not descriptive of organic heart disease.

3, History of one or more attacks of a major rheumatic manifestation; no physical signs to suggest a valvular defect.

4, No definite history of a major rheumatic manifestation; well-defined valvular defects, *including mitral stenosis.*

5, No definite history of a major rheumatic manifestation; well-defined valvular defects, *not including mitral stenosis.*

*In 20 of these valvular lesion, also, preceded major manifestation.
M. & J., muscle and joint.

pendable records. 2. A social worker* attempted to bring back to the clinic, at least once, those who were no longer in actual attendance in order to obtain interval histories and examinations. 3. Of patients treated during the interval in other hospitals or convalescent homes, information was gathered from interviews with the family or family physician, a perusal of the hospital records, autopsy reports, or death certificates. In this group we included cases only when the original records contained dependable information.

Distribution According to Sex.—There were 240 (49.2 per cent) males and 248 (50.8 per cent) females. This distribution is similar to that in the entire rheumatic group as well as in that of the basic group of

TABLE II

AGE AT BEGINNING OF OBSERVATION

AGE	NO.	PER CENT	CUMULATIVE PER CENT
2	1	0.2	0.2
3	8	1.6	1.8
4	10	2.0	3.8
5	17	3.5	7.3
6	24	4.9	12.2
7	41	8.4	20.6
8	46	9.4	30.0
9	52	10.7	40.7
10	55	11.3	52.0
11	53	10.9	62.9
12	65	13.3	76.2
13	47	9.7	85.9
14	42	8.6	94.5
15	19	3.9	98.4
16	6	1.2	99.6
17	2	0.4	100.0
	Total 488	100.0	
Mean 10.1 years			

1,107 cases. In the whole rheumatic group there were 344 (45.9 per cent) males and 406 (54.1 per cent) females. In the basic group there were 532 (48.1 per cent) males and 575 (51.9 per cent) females.

Age at Beginning of Observation.—In studying juvenile rheumatic heart disease the group selected should be representative of childhood. Initial observations should be begun before puberty. Observations first undertaken at a later age preclude the probability of obtaining dependable histories. Statements made later are often vague with reference even to major manifestations. Earlier histories are likely to contain records of milder flares, since the initial affection may date back only two or three years.

*A full-time social worker was assigned for about two years to locate patients who could not be reached by the usual means of communication. Contact was often made through such indirect channels as interviews with former neighbors and relatives; through records of other hospitals and clinics; or through other social service agencies. We are indebted to Mrs. Henry F. Glazer and to the Social Service Auxiliary of Mount Sinai Hospital for the social worker who was assigned to assist in this study. Statisticians and clerical aid were provided by the Research Committee of the New York Heart Association.

The age at first observation was in most cases within the period of childhood (Table II). The mean age was ten years. Twenty-five per cent were first examined before 7.5 years of age, and an additional 50 per cent between 7½ and twelve years of age. Over 94 per cent were under observation on attaining fourteen years of age.

Interval Between Initial Rheumatic Manifestation and Beginning of Period of Observation.—The patients came under observation at varying intervals after their initial major rheumatic affection (Fig. 1). Most of them, however, were first observed either during the same year as, or a few years after, the initial episode. In a few isolated

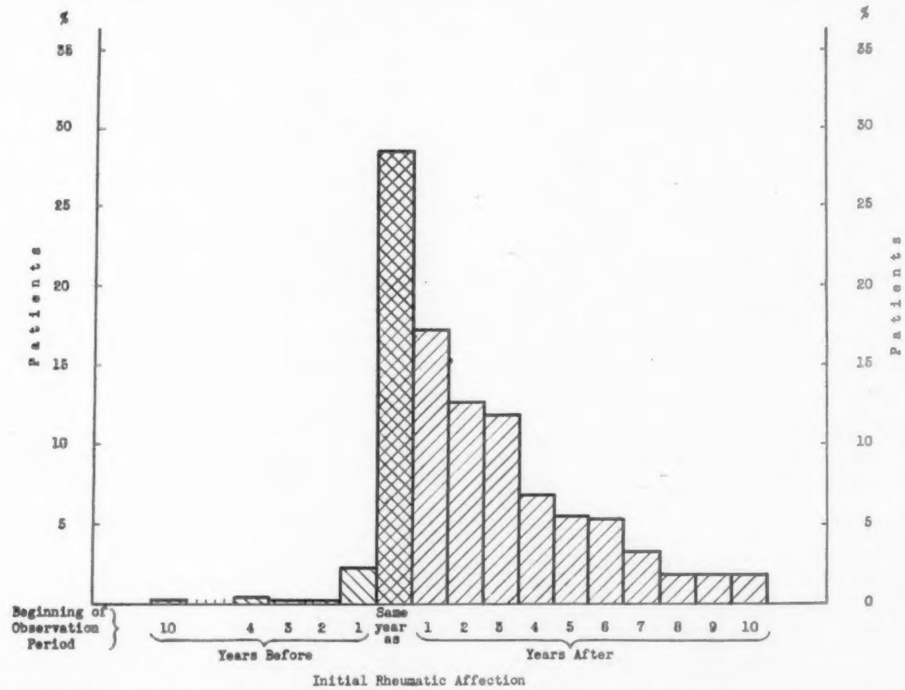

Fig. 1.—Interval between initial rheumatic manifestation and beginning of period of observation.

cases observation began from one to ten years before the first major rheumatic affection, but this number was negligibly small (11, or 3.3 per cent). A far greater number (28.5 per cent) was observed during the year of initial affection than in any other year. Next in frequency were those who came under observation one, two, and three years later. The mean interval between the year of initial affection and the year of first observation was two and three-tenths years.

Duration of Observation Since Initial Rheumatic Manifestation.—The interval between the initial affection and the end of the period of observation in this selected group averaged eight years (Fig. 2). Since these children came under active clinic care about two years

after their first affection (see preceding section), the period during which the course of the disease has been actually observed is less than six years. However, since the disease was ushered in by a major rheumatic affection in all these children, the majority had been attended either in hospitals or by private physicians. The records give satisfactory information, therefore, of the length of the period between initial episode and first observation. Eight years, consequently, may be considered as the mean duration of observation.

Initial Major Rheumatic Affections, Grouped According to Type.—*Polyarthritis* was the most common type of initial affection (Fig. 3). It was present in 66 per cent (322) of cases. It was the only apparent affection in 45 per cent (220). Associated with carditis, it was present in 16 per cent (79); and with chorea, in 4 per cent (18).

Carditis was present in 32 per cent (158) of cases. It appeared alone in 14 per cent (68). The remaining cases were associated mainly with

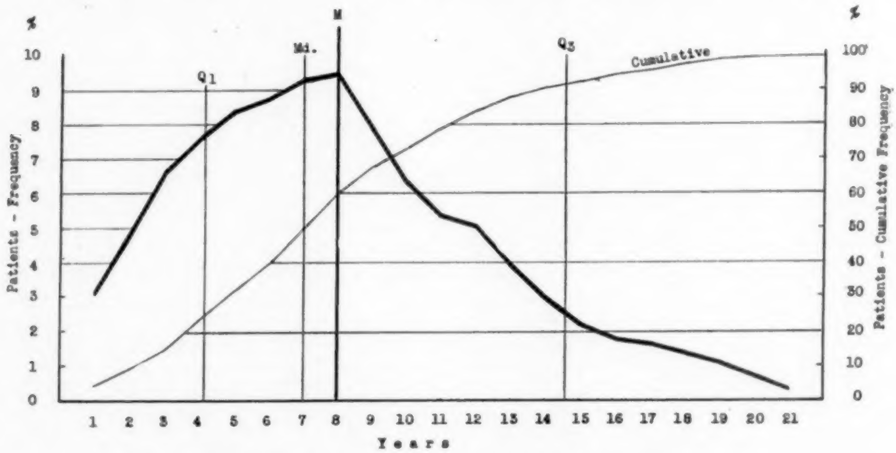

Fig. 2.—Duration of observation since initial rheumatic affection.

polyarthritis, that is to say, in 16 per cent (79), as already stated. Carditis was associated with chorea in only 1 per cent (6).

Chorea was present in 25 per cent (121). It occurred alone in 19 per cent (92). Its association with polyarthritis and carditis has already been mentioned.

A combination of the three major rheumatic affections as an initial manifestation was rare. It occurred in only 1 per cent (5).

Types of Initial Affections by Sex.—When the sexes are considered separately, polyarthritis was the most common initial manifestation of the disease in girls as well as boys. However, one and one-half times as many girls as boys exhibited chorea as the first evidence of rheumatic affection (Fig. 4). A concurrence of chorea and carditis was observed somewhat more often among girls than boys. The number of these cases, however, is far too small to permit of any generalization.

AGE AT ONSET OF MAJOR RHEUMATIC AFFECTIONS

The age at onset of juvenile rheumatism has been studied over many years, especially in England and the United States. We have found

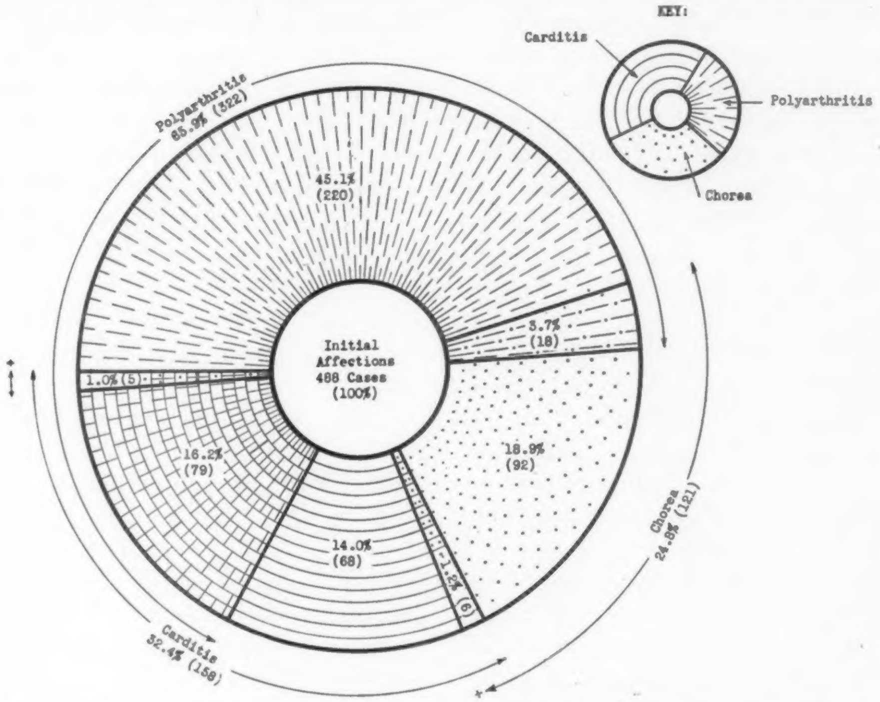

Fig. 3.—The number of cases in each initial major rheumatic affection according to type.

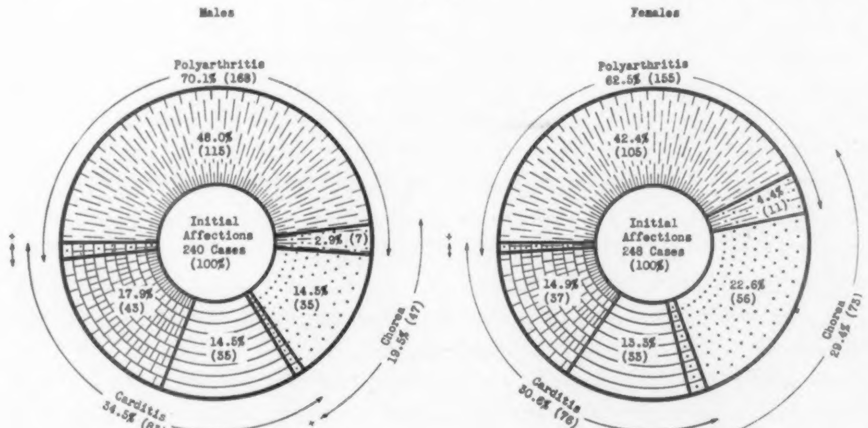

Fig. 4.—The number of cases in each type of initial affection by sex.

no reports in the literature dealing with groups of patients in whom the initial manifestations of the disease consisted exclusively of major rheumatic episodes, which would make them comparable, however, to the data presented in this paper.

In the literature the age at onset is generally regarded in a broad sense as representing an age period. Most writers refer to the span five to fifteen years as the period of greatest incidence of first manifestations of rheumatism.[1, 2, 3, 4, 5] Some narrow the age group down to the years seven to twelve,[6] while still others limit it to the age period ten to twelve years.[7]

The *mean* age at onset, as given in the literature, ranges from about seven years[8, 9, 10] to as high as nine years.[3]

The *mode* or year of greatest incidence varies similarly in different reports. The most common estimate is the seventh or the eighth year.[2, 8, 10, 11, 12] Some have found it as low as the sixth or the seventh year.[13] In contrast to these, one report, based on 1,000 cases compiled over some thirty years, concludes that the highest incidence of "rheumatic heart disease" is "around the tenth year." This author[14] states, in addition, that the incidence of acute rheumatism is relatively infrequent before five years of age, although it is his impression that the disease is more frequent than is generally recognized. He adds a review of 100 cases of acute juvenile rheumatism which he observed. Among these he found that 13 per cent had their first attack between the ages of three and five years.

The discrepancy in the literature is due to several factors. Not only the size of the groups but also the age limits of the groups vary widely with different reports. Some groups consist of only 50 cases;[4] others are as large as 1,000 cases.[14] The age groups in some reports are limited to children below ten years of age,[10, 11] while in others the study includes not only children and young adults but also the aged.[5, 14] Perhaps even more important than these is the utter lack of uniformity in criteria in the literature as to what constitutes acute rheumatism. Equally difficult is the task of tracing the initial episode when the disease takes an ill-defined form. Some authors compile their rheumatic series on the basis of "rheumatic pains,"[11] which include "growing pains" as well as "pain and swelling of the larger joints," and "rheumatic carditis" which turns out to be valvular lesions without any "other manifestation of rheumatism." Others[14] deal with the incidence of "rheumatic heart disease" only. Still other authors,[5] by including cardiac involvement as evidence of active rheumatism, base their diagnosis on such findings, at times, as tachycardia, cardiac enlargement, extrasystoles, or murmurs. With the assumption that in isolated cases such findings are of diagnostic importance in that they help to round out a clinical picture of acute carditis, it must still be admitted that there is no uniform agreement among different investigators as to the actual significance of these findings.

Finally, there still remains the problem of a careful compilation of statistical data and the interpretation of graphic records. In an attempt to arrive at a figure representing the average age in childhood

at which rheumatic affection begins, two points must be kept in mind: first, the size of the sample, and second, its constitution. Obviously, in a relatively small sample, particularly such as is usual in the experience of a single observer, even after many years of experience, the *mean* (arithmetic average) is affected by a few extreme cases at either end of the scale. Before placing too great dependence on the mean, the whole curve must, therefore, be taken into consideration, and the *mode* (the age at which the greatest incidence occurs) should be considered as possibly more typically descriptive of the series. Furthermore, the samples must be homogeneous to such a degree as will make the comparisons valid. The age limits included in any

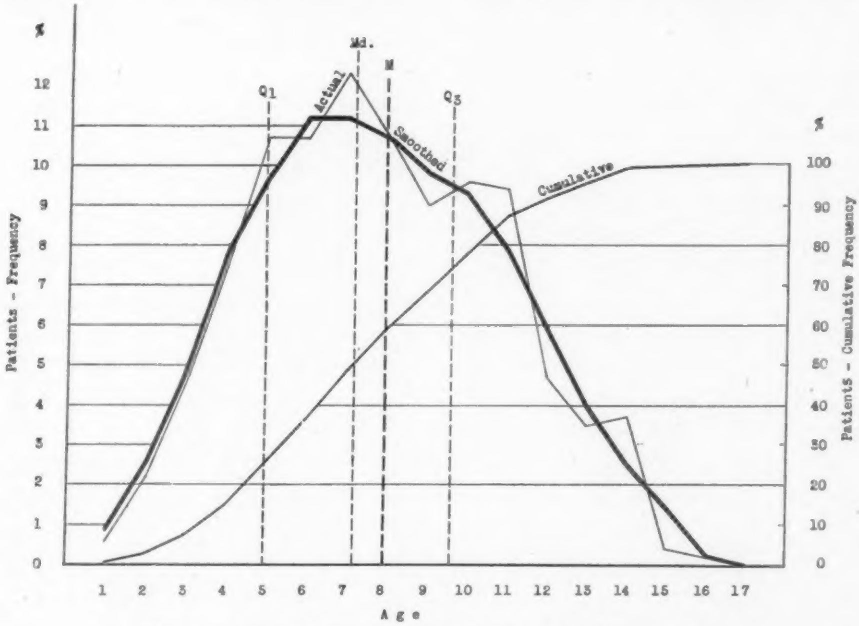

Fig. 5.—Age at onset of the major rheumatic affections.

given series of cases naturally affect the mode as well as the mean. A sample that is drawn from a clinic in which the upper age limit for admission is twelve years will, for instance, present a different curve from one in which the upper age limit is sixteen years. An average, to be useful, must be typical of actual conditions. These are factors that must be kept in mind when comparing the observations reported by different authors.

Age at Onset in the Group Selected for This Study.—The mean age at first manifestation of juvenile rheumatism in our group of 488 children in whom the disease was ushered in by a major manifestation was eight years, and the mode, or highest incidence, was at seven years (Fig. 5). The smoothed curve shows the height of incidence as early as the sixth year. This height is practically maintained up

to the age of eight years, after which the curve slopes gradually. It is interesting to note that 26 per cent of this group experienced a first rheumatic affection within the first five years; 36 per cent within the first six years; and that as many as 78 per cent already presented a first affection by the end of the tenth year. In over 90 per cent the age at onset was less than twelve years. In other words, in one-fourth of the children the initial major rheumatic affections appeared within the preschool age, and in most of the remaining three-fourths it occurred before the thirteenth year.

It is possible that our group is distinctive only in that it represents cases in which the disease had a stormy onset, while the groups studied by other writers represent those cases also in which the disease had

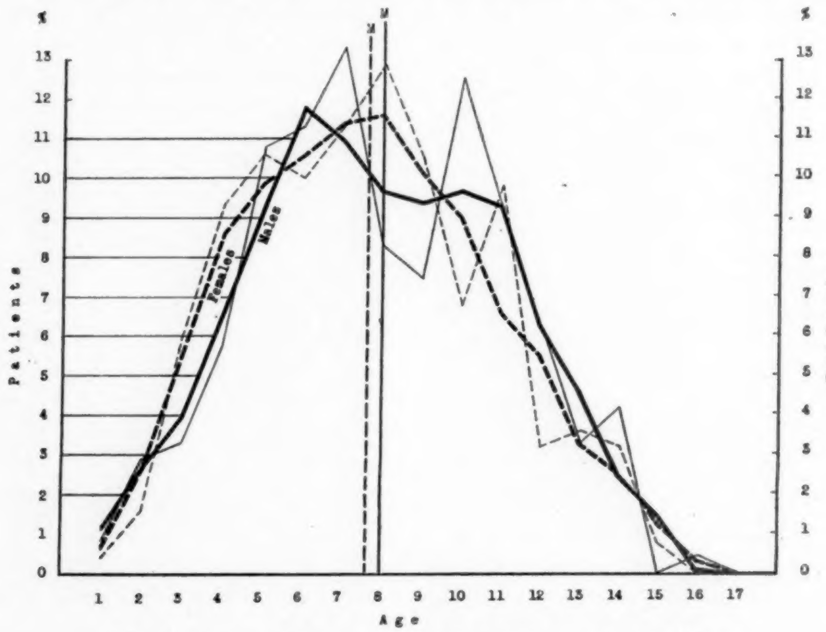

Fig. 6.—Age at onset of the major rheumatic affections by sex.

an insidious onset. The agreement in the age incidence of first affections between our group and some of those reported suggests that, generally speaking, the so-called rheumatic pain may very well be the first manifestation of rheumatism in childhood.

A further analysis brings out several interesting features of the disease, not quite apparent in a general survey of the subject. We find, for instance, that the mean age at onset is very close for the two sexes (Fig. 6). It is slightly earlier for girls than boys. But the mode or highest incidence of initial rheumatic affections is at a definitely earlier age in the case of boys. First affections among boys occurred in greater numbers at about six years than at any other age, while in girls, the highest incidence was reached during the eighth year.

Age at Onset for Patients Grouped According to the Type of the Initial Rheumatic Affection.—Far more revealing is the analysis of the age at onset for the different clinical *types* of first affections—polyarthritis, carditis, carditis with polyarthritis, and chorea (Fig. 7). We find that the mode or the highest incidence of a first manifestation of these major affections varies definitely with the type of the affection. For polyarthritis as a first affection the mode is reached at about the age of five years; for carditis, at six years; while for chorea it is delayed to the ages of seven and eight years. Furthermore, while polyarthritis and carditis occur in at least 20 per cent of cases in the

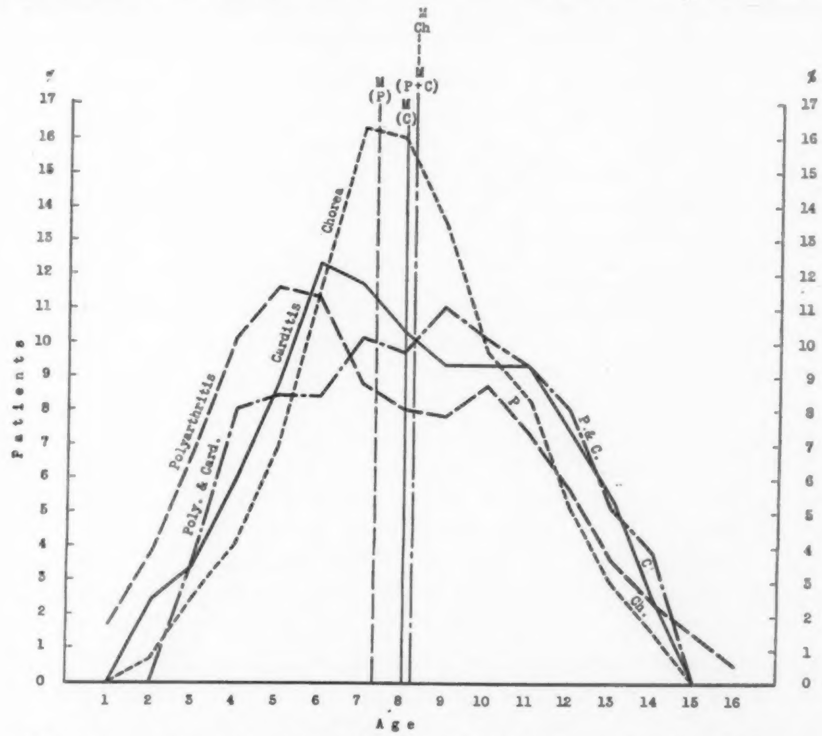

Fig. 7.—Age at onset in each clinical type of the major rheumatic affections.

preschool ages, the curves depicting the incidence for these affections tend to continue more or less high up to ten and twelve years. Chorea, on the other hand, occurs in only 13 per cent in the preschool ages, but its curve reaches a conspicuous peak at seven and eight years. The delay of the mode in the curve for chorea as a first manifestation explains why the highest incidence for all first affections is later for girls than for boys (Fig. 6). Chorea was found to be a more common first affection among girls than among boys, proportionately as 73 to 47 (Fig. 4).

The curve of concomitant affections of polyarthritis and carditis follows that of either polyarthritis or carditis, although the incidence

by year of this dual affection is highest between seven and eleven years. Both polyarthritis and carditis, as individual affections, seem to have a slight secondary rise in incidence as first affections at ages nine and ten years.

In our group then, initial rheumatic manifestations, consisting exclusively of acute attacks of polyarthritis, carditis, or chorea, or any combination of these, occurred at a rather early age. Our records show, furthermore, that the age period at which the onset of the disease reaches its greatest incidence varies appreciably with the different clinical types of initial affections. The age incidence for polyarthritis and carditis as first manifestations reaches a peak before or at the age of school entrants. We note, furthermore, that these affections play a significant rôle not only during the preschool age but also during the ages up to puberty. Chorea, on the other hand, while present in fair numbers during the same periods, takes a decided lead at ages seven to ten years, and its incidence at this time proportionately overshadows the other affections as a first manifestation of juvenile rheumatism.

Of course, believing as we do that major affections are not the only manifestations of active juvenile rheumatism and that many of the major episodes are preceded by and at times considerably antedated by less conspicuous clinical signs (exclusive even of muscle and joint pains), our observation of this special group leads to the assumption that acute rheumatism in children has its onset at a far earlier age than is generally implied in literature on the subject. Even though the disease is found at all ages, statistical curves, compiled for no matter how many age groups, still show that the incidence of first manifestations is highest during childhood. Clearly, it requires an intimate study of children's groups to indicate how early the disease really begins. If in coming years our familiarity with the "minor" symptoms and signs of juvenile rheumatism becomes greater, and if dependable diagnostic tests come to our aid, the disease may be found to have its onset among the earliest diseases of childhood.

RECURRENT MAJOR RHEUMATIC AFFECTIONS

Because of the protean manifestations of juvenile rheumatism, particularly because of its frequently protracted clinical course, the question is asked, what is a recurrence? This question is embarrassing in view of the fact that no adequate criteria exist to decide when the disease begins or when it actually terminates. Obviously, clinical criteria, in order to be serviceable, must define a recurrence as a clearly distinguishable event far enough removed from a preceding episode to preclude the likelihood of its being merely a continuation. Even this criterion is unsatisfactory in a disease which has a tendency to follow a polycyclic course. Any criterion is, in fact, arbitrary.

When an acute rheumatic affection was located, especially at the beginning or at the end of a year, the records of the year preceding or following it were examined, to be certain the episode was an isolated major affection. In order that the second attack might qualify as a recurrence, several months of apparent well-being must have elapsed during which a child was ambulatory, attending school or on a vacation. An uninterrupted episode even of two years' duration was regarded as a single attack.

Average Duration of Observation After the Initial Affection in Patients With and Without Recurrences.—In estimating the meaning of recurrences, the average duration of observation since the beginning must be known, particularly in relation to types of initial affection. Those without recurrences may not have survived or have been observed long enough to experience a recurrence. For comparison the mean duration of observation in both groups has, therefore, been tabulated, and for each subgroup according to the type of the initial affection (Table III).

TABLE III

AVERAGE DURATION OF OBSERVATION AFTER THE INITIAL AFFECTION IN PATIENTS WITH AND WITHOUT RECURRENCES

INITIAL MANIFESTATION	GROUP WITH RECURRENCES YEARS	GROUP WITHOUT RECURRENCES YEARS
Polyarthritis	9.0	7.3
Chorea	8.7	7.0
Carditis	7.3	5.4
Polyarthritis and carditis	7.5	8.3
Total group	8.5	7.1

For the entire group the average length of observation since the onset has been 8.5 years in patients with recurrences and 7.1 years in those without recurrences. The shortest period occurred in the subgroup *carditis*, particularly in those without recurrences. But even in these, the period has already exceeded five years. That this period affords ample time for a recurrence to take place will be shown in a subsequent paragraph.

TABLE IV

THE INCIDENCE OF A MAJOR RECURRENCE DURING THE PERIOD OF OBSERVATION IN THE ENTIRE GROUP AND IN SUBGROUPS, ACCORDING TO TYPE OF THE INITIAL AFFECTIONS

INITIAL MANIFESTATION	TOTAL PATIENTS	PER CENT	NUMBER WITH RECURRENCES	PER CENT
Polyarthritis	220	100.0	149	67.7
Chorea	92	100.0	68	74.0
Carditis	68	100.0	40	58.8
Polyarthritis and carditis	79	100.0	49	62.0
Polyarthritis and chorea	18	100.0	15	83.4
Chorea and carditis	6	100.0	5	83.3
Polyarthritis, carditis, and chorea	5	100.0	5	100.0
Total group	488	100.0	331	67.8

Major Recurrences and Their Frequency in the Period of Observation.—More than two-thirds of the patients, 68 per cent (331), experienced at least one recurrence during an average of eight years (Table IV). The number varied according to the type of the initial affection. A recurrence was most common in *chorea* (74 per cent). So far, only about one-quarter of these children escaped. Next in order of frequency was the subgroup *polyarthritis* or *polyarthritis with carditis* (67.7 per cent and 62 per cent, respectively). In the subgroup *carditis* recurrences appeared in 58.8 per cent. In the combined affections the number was too small to warrant further study.

The number of recurrences (Table V) in individual cases differed widely. In the majority there was only one or two, but in an appreciable number there were three, four, or five. In a few cases there were six or more.*

TABLE V

NUMBER OF RECURRENCES IN INDIVIDUAL CASES

NUMBER OF RECURRENCES	NUMBER OF PATIENTS	PER CENT OF PATIENTS	CUMULATIVE PER CENT
1	128	38.7	38.7
2	89	26.9	65.6
3	58	17.5	83.1
4	22	6.6	89.7
5	20	6.0	95.7
6	8	2.4	98.1
7	2	0.6	98.7
8	1	0.3	99.0
9	0	-	99.0
10	2	0.6	99.6
11	1	0.3	99.9
Total	331	99.9	99.9

Interval Between the Initial Affection and a First Major Recurrence.—As has been stated, a first recurrent major affection was observed in 331 cases in the course of an average period of observation of eight years:

44 per cent (145) within one year of the initial affection;
20 per cent (67) in the course of the second year; and
9 per cent (31) during the third year.

Recurrences appeared, therefore, within three years after the initial manifestation of the disease in 73 per cent (243) (Fig. 8).

*Two cases presented ten and one case eleven major recurrences in the course of twelve and thirteen years. These cases being unusual, a brief description of the clinical course presented by one patient is given: J. G., a female, suffered at the age of four years an attack of polyarthritis for one week in winter; at the age of six years chorea appeared for two months in the autumn, and polyarthritis for one and a half weeks in winter; at the age of seven years chorea returned for two months in the autumn; at the age of eight years there was another attack of chorea for two months in the autumn; at the age of nine years, again, an attack of chorea for two months in the autumn and of polyarthritis for two weeks in winter; at the ages of ten and eleven years, another attack of chorea for two months in the autumn during each year; at the age of twelve years, chorea again for two months in the autumn and polyarthritis in winter; at the age of thirteen years, polyarthritis in the spring; at the age of fourteen years, carditis with adhesive pericarditis for seven months, from January to August; and at the age of sixteen years, severe rheumatic carditis for one month in the autumn resulting in death.

In a similar manner the time interval between the initial affection and the first recurrence in the several subgroups was analyzed. Of 220 patients with *polyarthritis,* 149 experienced at least one major recurrence:

38 per cent (57) within one year of the initial affection;
18 per cent (27) during the second year; and
7 per cent (11) during the third year.

In this subgroup, then, recurrences had appeared in 63 per cent (95), by the end of three years following the initial affection (Fig. 8).

In the subgroup *carditis,* of 68 patients, 40 experienced at least one major recurrence:

57.5 per cent (23) within one year of the initial affection;
15.0 per cent (6) during the second year; and
12.5 per cent (5) in the course of the third year.

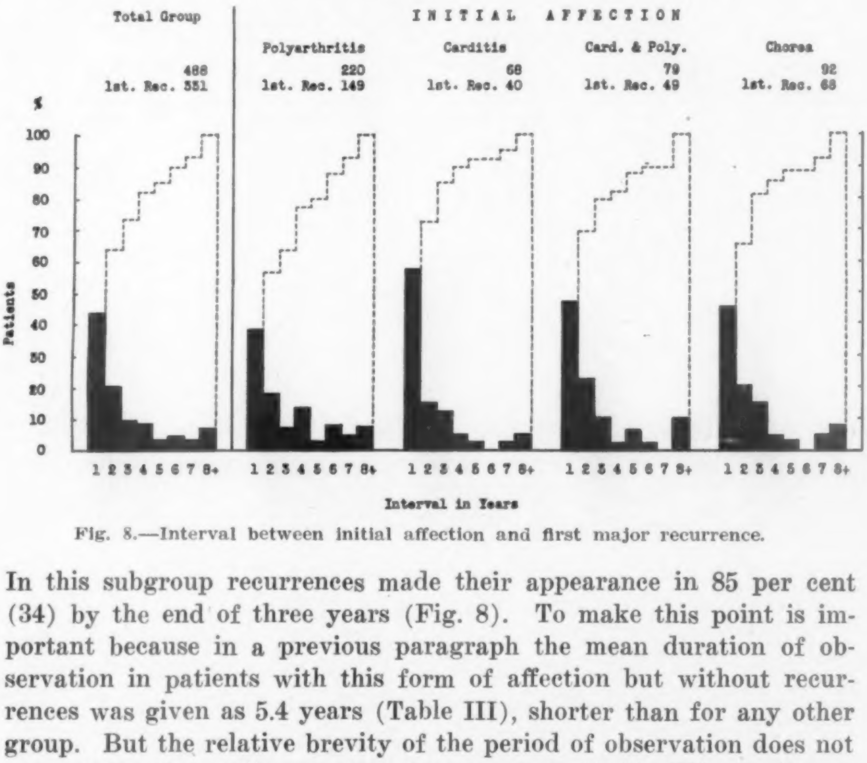

Fig. 8.—Interval between initial affection and first major recurrence.

In this subgroup recurrences made their appearance in 85 per cent (34) by the end of three years (Fig. 8). To make this point is important because in a previous paragraph the mean duration of observation in patients with this form of affection but without recurrences was given as 5.4 years (Table III), shorter than for any other group. But the relative brevity of the period of observation does not account for the smaller number of recurrences (Table IV), for 90 per cent occurred before the expiration of five years.

In the subgroup (79 cases) in which *carditis and polyarthritis* were combined there were 49 recurrences:

47 per cent (23) within one year after the initial affection;
23 per cent (11) during the second year; and
10 per cent (5) during the third year.

Here 80 per cent (39) occurred within three years (Fig. 8).

In the subgroup *chorea* (92 cases), the number of recurrent affections was 68:

46 per cent (31) within a year following the initial attack;
21 per cent (14) during the second year; and
15 per cent (10) during the third year.

In this subgroup recurrences appeared in 82 per cent (55) within three years (Fig. 8).

Interval Between the Initial Affection and a Second Major Recurrence.—The time of second recurrences has also been analyzed (Fig. 9). These took place in 198 (40 per cent):

35 per cent (69) appeared within two years after the initial attack;
16 per cent (32) in the course of the third year; and
11 per cent (21) during the fourth year.

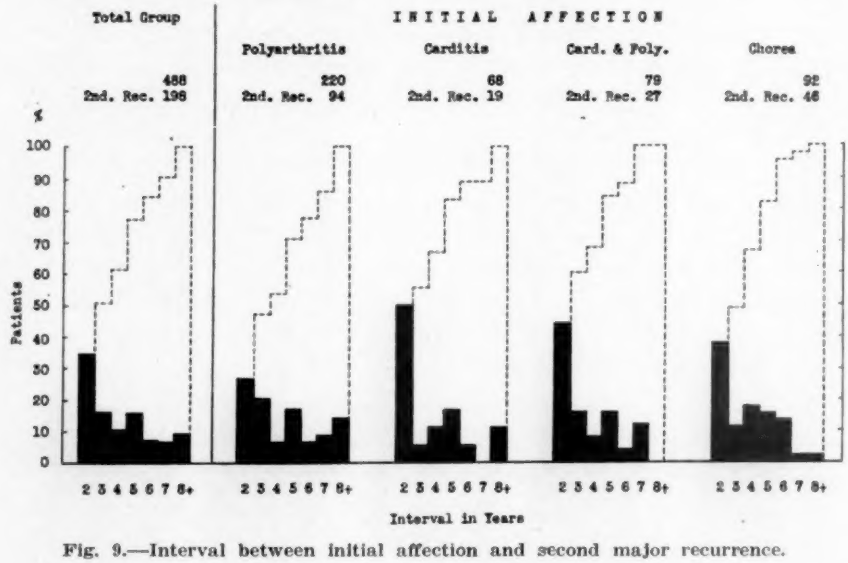

Fig. 9.—Interval between initial affection and second major recurrence.

Sixty-two per cent (122), or almost two-thirds, appeared by the end of four years. When a major recurrent affection appeared within one year after the initial attack, it was not regarded as a second recurrence.

Second recurrences in each of the subgroups need not be described in detail. The numbers are too small. The facts are presented, however, in Fig. 9. It is apparent that second recurrences are not crowded into the years immediately following the initial affection as are the first recurrences. What is significant is that they appear in appreciable numbers as late as four, five, or even six years after the onset of the disease.

The Factor of Personal Susceptibility.—From the data on first and second recurrent affections, particularly with reference to the order

of their appearance in successive years following the initial affection, it becomes apparent that attacks of juvenile rheumatism have a great tendency to recur. It is obvious, furthermore, that by far the greatest number appear within a few years after the onset of the disease. One-third to one-half of the first recurrences made their appearance within one year; and approximately three-quarters not later than three years after the initial affection. Second recurrences naturally appeared later. Nevertheless, among these, too, approximately two-thirds appeared within four years.

Two interpretations are possible. In the first place, so-called recurrences may be in reality not distinct and separate episodes, but merely exacerbations of silent or smoldering processes. But, applied to the data now reported, this conception assumes that juvenile rheumatism runs a continuous course for two or more years in at least one-third of the cases and for three or more years in one-quarter of all cases. While the disease undoubtedly runs a long-drawn-out course in an appreciable number of cases (such cases have been reported[15]), unsupported experience does not lead to the conclusion that cases of several years' duraton are as common as the records suggest, counting recurrent major episodes merely as recrudescences. One-quarter of the first recurrences failed, indeed, to appear for three years. First recurrences sometimes appear so many years after the initial attack that a true recurrence* of the disease must be assumed. Recurrence did not, in fact, appear in 5 to 10 per cent of cases, for as long as eight years or more (Fig. 8).

According to the second interpretation, later attacks may be not recrudescences but distinct, new infections. Their appearance in the first few years after the initial manifestation is taken to indicate that there is increased susceptibility to new invasion. Seasonal recurrences, as well as their tendency to follow in the wake of intercurrent diseases, especially of the upper respiratory type, lend plausibility to this assumption. This view is strengthened, furthermore, by the well-known fact that patients migrating to subtropical climates are generally free from this disease, although on returning to their former homes, even after several years, they are subject, not uncommonly, to new attacks.[16, 17]

Obviously in the present state of knowledge the nature of recurrent attacks of juvenile rheumatism is not understood.

The Relation of Types of Recurring Attacks to the Type of the Initial Affection.—With the hope of shedding more light on the nature of recurrent manifestations of juvenile rheumatism, the recurrences themselves have been grouped according to clinical types.

*A true recurrence may be likened to what is analogously termed a "superinfection" in tuberculosis.

Polyarthritis.—In 220 cases of initial *polyarthritis,* recurrences appeared in 149 cases and second recurrences in 94 cases (Figs. 8 and 9).

Among the 94 *second recurrences* (Fig. 10*A*) polyarthritis was present, alone or combined, in 74 per cent (110 cases). It was the only affection in 55 per cent (82). It was associated with acute carditis in 24 cases, and with chorea in only 3 cases. Acute carditis was the next most common. It was present alone in 17 per cent (25) and combined with polyarthritis in 16 per cent (24). Chorea was pres-

SUB-GROUP IN WHICH POLYARTHRITIS IS THE INITIAL AFFECTION

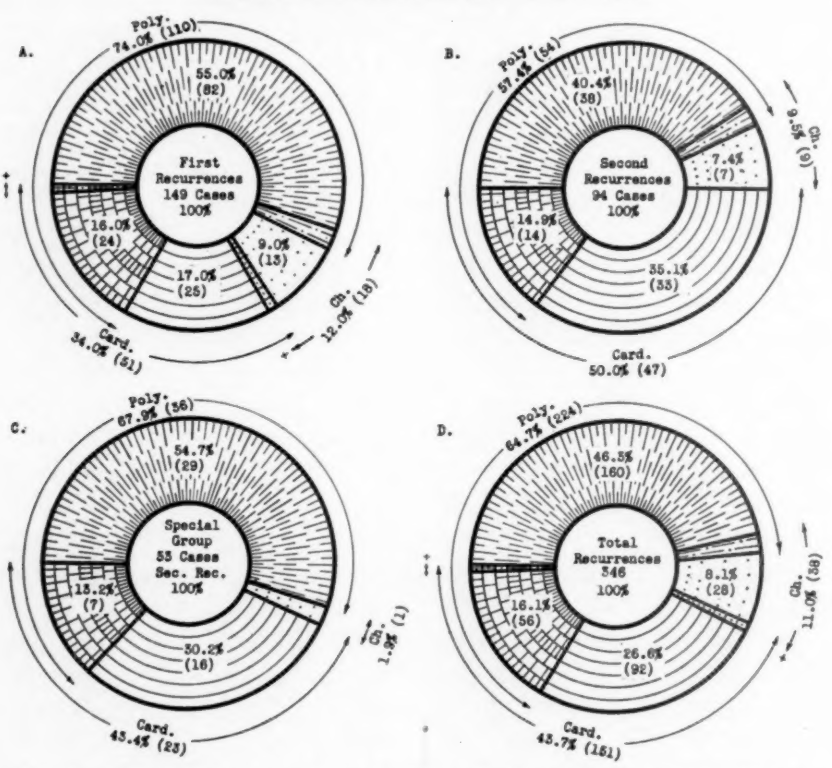

Fig. 10.—Clinical types of recurrent major affections related to *polyarthritis* as initial affection.

Of 220 patients with primary *polyarthritis,* 149 experienced at least one recurrence of a major manifestation, *A,* and 94 exhibited a second recurrence, *B.* Fifty-three patients (of the 82 shown in *A*) are constituted a "special" group because they exhibited a major episode three times, the initial attack and the first recurrence being *polyarthritis, C. D* presents the types of a total of 346 recurrent manifestations experienced by 149 of the 220 patients in whom one or more recurrences appeared during the period of observation.

ent alone in only 9 per cent (13). In 5 additional cases it was combined with the other affections.

Among the 94 *second recurrences* (Fig. 10*B*) polyarthritis was present in 57 per cent (54). It appeared alone in 40 per cent (38), and combined with carditis in 15 per cent (14). Acute carditis was al-

most as common a second recurrence as polyarthritis, appearing alone in 35 per cent (33), and associated with polyarthritis in 15 per cent (14). Chorea appeared among the second recurrences of this group in only 9 cases, or in less than 10 per cent.

Second recurrences were next examined in a *special group* of 82 cases, characterized by the fact that both the *initial attack* and the *first recurrence* were polyarthritis. In this group a second recurrence appeared in 53 cases (Fig. 10*C*). While the group is small, it is im-

SUB-GROUP IN WHICH CARDITIS IS THE INITIAL AFFECTION

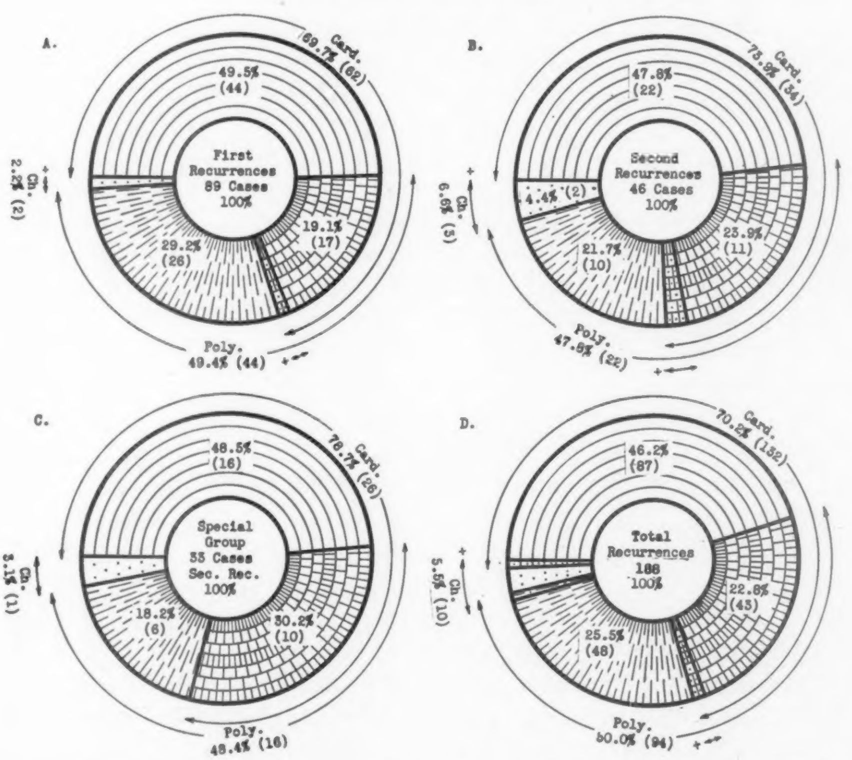

Fig. 11.—Clinical types of recurrent major affections related to *carditis* as initial affection.

Of 147 patients with primary *carditis* (with or without polyarthritis), 89 experienced at least one recurrence of a major manifestation, *A*, and 46 exhibited a second recurrence, *B*. Thirty-three patients (of the 44 shown in *A*) are constituted in a "special" group because they exhibited a major episode three times, the initial attack and the first recurrence being *carditis*, *C*. *D* presents the types of a total of 188 recurrent manifestations experienced by 89 of the 147 patients in whom one or more recurrences appeared during the period of observation.

portant that 55 per cent (29) again presented polyarthritis. Carditis appeared in 30 per cent (16) and polyarthritis with carditis in 13 per cent (7). Chorea appeared only once. Accordingly, the second recurrences constituting, in fact, the third major episode consisted almost

entirely (98 per cent) of polyarthritis, carditis, or both. Although there was a high incidence of carditis throughout, polyarthritis stood out as the predominant affection.

Carditis.—Because in the group of initial polyarthritis, carditis alone or in combination was a common recurrence, the group of initial *carditis* alone or combined with polyarthritis was also investigated. There were 147 such cases (68 cases of carditis alone and 79 cases of carditis with polyarthritis), in which 89 first and 46 second recurrences were traced (Fig. 11*A* and *B*).

Of 89 *first recurrences* (Fig. 11*A*) carditis appeared alone in 50 per cent (44); polyarthritis alone in approximately 30 per cent (26); and a combination of carditis with polyarthritis in 20 per cent (17). Chorea was present in 2 cases only, in one case alone and in one case with carditis.

Among the 46 *second recurrences* (Fig. 11*B*) carditis appeared alone in 48 per cent (22); polyarthritis alone in 22 per cent (10); carditis with polyarthritis in 24 per cent (11); and chorea in 3 cases only. In 2 cases it appeared alone, and in a third case it was associated with carditis and polyarthritis. In this group, too, when carditis, either alone or in association with polyarthritis, was the initial affection, both carditis and polyarthritis reappeared as the dominant affections among first and second recurrences to the extent of 98 per cent and 93 per cent, respectively.

Chorea.—In a similar manner the subgroup in which *chorea* was the initial manifestation has been investigated. Of 92 cases, 68 exhibited at least one recurrence and 46, two recurrences (Fig. 12).

Of the *first recurrent affections* chorea appeared alone in 70.5 per cent (48); with carditis, in 6 per cent (4); and with polyarthritis, in 3 per cent (2). Acute carditis appeared alone in 7 per cent (5) and polyarthritis alone in 12 per cent (8). Altogether chorea made its reappearance in 79 per cent (54) (Fig. 12*A*).

The *second recurrences* were equally impressive. Here again the initial affection chorea reappeared. It holds true in 78 per cent (36). These were all, except one, clinically uncomplicated cases of chorea. In the remaining 10 cases polyarthritis was present in 6, and acute carditis in 4 cases (Fig. 12*B*).

As before, a *special group* of 48 cases was studied in which chorea appeared as the *initial* as well as the *first recurrent* affection. A third major episode occurred in 36 (Fig. 12*C*), of which 81 per cent (29) were chorea alone, 8 per cent (3) each polyarthritis and carditis, and 1 case chorea with carditis.

These observations are recapitulated in tabular form for the sake of giving a general summary (Table VI).

The Factor of Susceptibility.—This analysis of the first and second recurrences reveals, it seems, convincingly, that major recurrences, the

first and second at any rate, are predominantly of the same clinical type as characterized the first manifestation of the disease. The disease usually remained true to type. When *polyarthritis* or *carditis* or both appeared as the initial manifestation of the disease, these affections reappeared to the extent of 91 per cent in first recurrences and 92.6 per cent in second recurrences (Fig. 10*A* and *B*). If, furthermore, the

SUB-GROUP IN WHICH CHOREA IS THE INITIAL AFFECTION

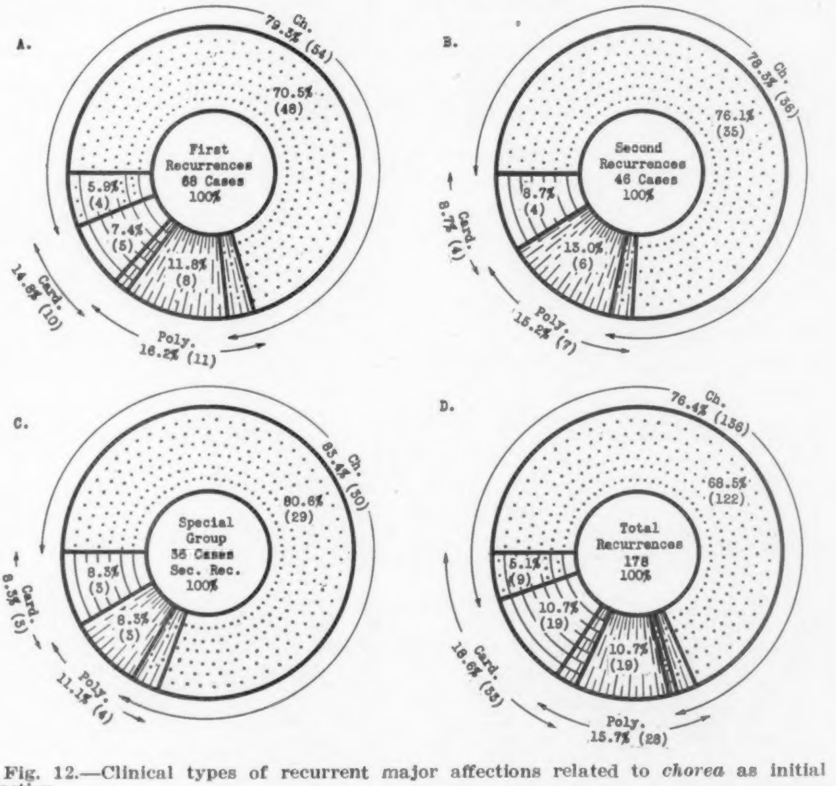

Fig. 12.—Clinical types of recurrent major affections related to *chorea* as initial affection.

Of 92 patients with primary *chorea*, 68 experienced at least one recurrence of a major manifestation, *A*, and 46 exhibited a second recurrence, *B*. Thirty-six patients (of the 48 shown in *A*) are constituted a "special" group because they exhibited a major episode three times, the first attack and the first recurrence being *chorea*, *C*. *D* presents the types of a total of 178 recurrent manifestations experienced by 68 of the 92 patients in whom one or more recurrences appeared during the period of observation.

initial affection and the first recurrence were polyarthritis, this type dominated the next recurrence or the third major episode almost exclusively.

The events are the same when *chorea* is the initial manifestation. The first and second recurrences are then predominantly chorea.

This striking tendency of recurrent affections to remain true to the initial pattern suggests that in juvenile rheumatism it is the state of the tissue which decides the form of the initial invasion and that it is

the state in which the tissue is left after the original attack which determines the subsequent clinical form of the disease. This statement, purposely put in this vague form, is as far as current evidence permits a deduction.

Clinical Types of All Major Recurrences.—Whether the appearances which were observed in the first and second recurrences are clinical types rather than acute exacerbations in the course of protracted forms of disease is open to doubt. If they are merely exacerbations,

TABLE VI

RECURRENCES OF MAJOR MANIFESTATIONS, SO FAR AS THEY REMAIN TRUE TO THE TYPE OF THE INITIAL MANIFESTATIONS

(RECAPITULATION OF FIGS. 10, 11, AND 12)

RECURRENCES		INITIAL MANIFESTATION					
		POLYARTHRITIS (220 CASES)		CARDITIS (147 CASES)		CHOREA (92 CASES)	
		NO.	%	NO.	%	NO.	%
First recurrence	Total patients	149	100.0	89	100.0	68	100.0
	Same type as initial manifestation	110	74.0	62	69.7	54	79.3
	Pure	82	55.0	44	49.5	48	70.5
	Complicated	28	19.0	18	20.2	6	8.8
Second recurrence	Total patients	94	100.0	46	100.0	46	100.0
	Same type as initial manifestation	54	57.4	34	73.9	36	78.3
	Pure	38	40.0	22	47.8	35	76.1
	Complicated	16	17.4	12	26.1	1	2.2
Second recurrence in special group*	Total patients	53	100.0	33	100.0	36	100.0
	Same type as initial manifestation	36	67.9	26	78.7	30	83.4
	Pure	29	54.7	16	48.5	29	80.6
	Complicated	7	13.2	10	30.2	1	2.8
All recurrences	Total incidence	346	100.0	188	100.0	178	100.0
	Same type as initial manifestation	224	64.7	132	70.2	136	76.4
	Pure	160	46.3	87	46.2	122	68.5
	Complicated	64	18.4	45	24.0	14	7.9

*This is a group in which the first recurrent affections (second major episodes) are pure clinical types, the same as the initial affections.

they would naturally resemble the phenomena at the time of the initial affection. Doubt is removed in part, however, since approximately 25 per cent of all first and 50 per cent of all second recurrences appeared not less than three years after the onset of the disease.

But the analysis was carried further. It included not only first and second, but all major recurrences throughout the period of observation. Recurrent major affections continued to be predominantly of the same clinical type as the initial manifestations.

In the subgroup *polyarthritis* (220 cases), 149 children experienced a total of 346 major recurrences (Fig. 10*D*). Polyarthritis, or carditis, or both were present 308 times (91.9 per cent). In 10 instances one or both of these affections were complicated by chorea. Uncom-

plicated chorea appeared only 28 times (8.1 per cent). This distribution resembles that in the first (91.0 per cent) and second (92.6 per cent) recurrences in the same subgroup.

In the subgroup *carditis,* with or without polyarthritis (147 cases), 89 children experienced 188 major recurrences (Fig. 11*D*). Among these, carditis, polyarthritis, or both were present 182 times (96.8 per cent). Four were complicated by chorea. Chorea alone was present only 6 times (3.2 per cent).

In the subgroup *chorea* (92 cases), 68 children experienced 178 major recurrences (Fig. 12*D*). Chorea reappeared 136 times (76.3 per cent). Fourteen were complicated by polyarthritis or carditis. Polyarthritis, carditis or both, uncomplicated by chorea, appeared 42 times (23.7 per cent).

In this form of analysis, also, the clinical type of the initial affection reappeared as the dominant type in approximately the same proportion as in first and second recurrences. This occurrence may be taken in connection with the remarks already made on the state of the tissue as an important factor in juvenile rheumatism.

The remarkable tendency of the original clinical form of the disease to reappear, year after year, occurs especially in cases in which the disease was ushered in by polyarthritis or carditis. Among the recurrences of this group, chorea was present in less than 10 per cent. When *polyarthritis* and *carditis* were the dominant clinical types, they reappeared in such large numbers and were so commonly associated as to suggest that they belonged essentially to one and the same clinical pattern.

In the subgroup *chorea,* on the other hand, though this manifestation was predominant in recurrent affections in its group (76 per cent), polyarthritis and carditis occurred as not uncommon complications. They were present alone, together, or in association with chorea, in over 30 per cent.

The relative rarity of chorea among recurrences in primary polyarthritis or carditis, in which valvular heart disease is known to be common, and the frequent appearance of polyarthritis and carditis as recurrences in primary chorea, in which valvular heart disease is reported as relatively rare, suggest that valvular disease in cases of primary chorea is due not to chorea, but to accompanying or intercurrent episodes of polyarthritis and carditis. Since it is believed that the latter appear, often not as easily recognized episodes such as have been termed "major manifestations" in this report, but in inconspicuous subacute form, their actual incidence in cases of primary chorea may be even greater than these statistics indicate. That this is the case may be inferred from the fact that these patients were referred to the cardiac clinic not because of chorea, but because heart disease was either present or suspected. Furthermore, in the cases of

primary chorea, in which polyarthritis or carditis appeared as major manifestations, mitral stenosis was three and one-half times as common as when these manifestations did not appear.

In the literature the incidence of cardiac involvement in chorea varies to such extreme degrees as to render any attempt at calculating its incidence a hopeless task. It is reported to be as low as 3 per cent,[18] and as high as 25 per cent[19] and even 60 per cent.[20] The marked divergence in opinion is due largely, it seems, to lack of uniform criteria as to what constitutes heart disease in the first place and, second, to difficulty in deciding when a case is really one of primary or pure chorea. If a rough estimate were attempted, nevertheless, the incidence of heart disease in cases of chorea would range between 30 and 40 per cent. This is approximately the percentage of major recurrent attacks of polyarthritis and carditis in our subgroup *chorea.* Valvular heart disease encountered in cases of chorea is probably due, in short, not to chorea but to accompanying or intercurrent episodes, often subacute, of polyarthritis and carditis.

SUMMARY AND CONCLUSIONS

This study is based on 488 cases, in each of which the onset of juvenile rheumatism was traced to a major episode, either polyarthritis, carditis, or chorea, or a combination of these, and the clinical course of which had been observed at the Children's Cardiac Clinic of Mount Sinai Hospital in New York within a period of fifteen years. There was only a slight difference in distribution according to sex.

The average interval between the *initial affection* and the time of *first observation* was 2.3 years; the average age at first observation was ten years; and the average duration between the initial affection and the end of the period of observation was eight years.

Polyarthritis was the initial affection in 322 cases; *carditis,* in 158 cases; chorea, in 121 cases. Combinations of these types, especially polyarthritis and carditis, were common. Polyarthritis was the most common initial affection for the entire group; chorea was one and one-half times as common among girls as among boys.

The mean *age at onset* was eight years and the mode was seven years. A more detailed analysis showed, however, that in fully one-quarter of the patients initial affections occurred in the preschool age. The mode varied with the clinical type characterizing the initial affection. In polyarthritis it appeared at about the age of five years; in carditis, at about six years; and in chorea, between seven and eight years of age. While the number of cases of polyarthritis and of carditis were at a relatively high level throughout the preschool as well as the entire school age, chorea appeared conspicuously crowded between the ages of seven and ten years (60 per cent).

During eight years, the average duration of the period of observation, at least *one recurrence* took place in 68 per cent; in the subgroup *chorea* 74 per cent had recurrences. In the majority of cases there were only one or two recurrences, but in an appreciable number as many as three, four, or five, and in a few cases six or more, were observed.

In the entire group, 73 per cent of first recurrences appeared not later than three years after the initial manifestation of the disease. In the subgroups they appeared within three years, as follows: in polyarthritis, 64 per cent; in carditis, 85 per cent; in carditis with polyarthritis, 80 per cent; in chorea, 81 per cent. At least two recurrences took place in approximately 40 per cent of cases. Nearly two-thirds of all second recurrences appeared not later than four years after the initial affection.

Juvenile rheumatism has, therefore, a great tendency to recurrences. For three or four years after its onset personal vulnerability is greatest. This has an important therapeutic implication. It suggests that a rheumatic child should be under close observation, in many cases preferably in an institution, for the first several years.

The question whether recurrences, especially the first and second, remained true to type was carefully studied. The analysis suggests that the type of the major recurrences is usually the same as that of the initial affection. Subsequent attacks of juvenile rheumatism appear, therefore, to depend on the original state or on the state subsequent to infection of the tissues. It is impossible now to come to a precise conclusion. An analysis of all the events which were observed confirms this deduction.

The tendency to remain true to type year after year is especially the case in polyarthritis and carditis. These manifestations are, furthermore, so frequently associated as to suggest that they express a similar method of response. Chorea reappears, nevertheless, with sufficient frequency to suggest that it is a distinct type, though polyarthritis or carditis is found not uncommonly among its recurrences.

It seems probable that the valvular heart disease which ultimately develops in cases in which the initial affection is chorea is due not to chorea but rather to polyarthritic and carditic manifestations associated with it or its recurrences. Further study of this problem is important.

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ATRIOVENTRICULAR RHYTHM WITH AND WITHOUT RETROGRADE BLOCK

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THE following case presents several unusual features which are of a clinical as well as of a physiological interest so that a short communication seems warranted.

REPORT OF CASE

Mrs. H., aged fifty-eight years, consulted me on Oct. 22, 1935, for palpitation of the heart. She had had a slow pulse for over twenty years; as long as her pulse rate was about 40-42 she felt well, but when the rate exceeded 48 she noticed palpitations which were associated with discomfort in her chest and head. She had diphtheria as a child and typhoid fever at the age of seventeen. In 1925 she consulted a well-known professor of medicine in Switzerland for pain in the right hypochondrium and for palpitation of the heart and slow pulse. It was found at the time that she suffered from chronic cholecystitis with hypercholesterinemia; an electrocardiogram taken at the time revealed that the bradycardia was due to a simple sinus bradycardia with a rate of 55 to 61 beats per minute (Fig. 1). For the past ten years after having taken repeated cures at Karlsbad and Vichy, and living permanently on a suitable diet, she had no trouble from her gallbladder. Another electrocardiogram taken in 1932 showed again sinus bradycardia, the rate now being 40 to 46; apart from a less marked S in Lead I and a different shape of P in Leads II and III, the tracing did not show any material difference in comparison with the record taken in 1925.

On examination I found the heart considerably dilated to the left, there was a sharp systolic murmur over the apex and the second aortic sound was accentuated and ringing. Heart and pulse rate was 44 per minute; the heart action was irregular, and on auscultation the arrhythmia gave the impression of being caused by numerous extrasystoles. Blood pressure was 140/80. The liver and the gallbladder were not palpable, and there was no tenderness in the right hypochondrium. The x-ray examination confirmed that the heart was dilated to the left and showed, moreover, a large left ventricle and a prominent aorta of increased density (Fig. 2). The retrocardiac space was free, the left auricle not enlarged. The urine was normal.

ELECTROCARDIOGRAMS

The first electrocardiogram taken the same day showed that the arrhythmia was not caused by extrasystoles but that this was a case of the comparatively uncommon "dissociation with interference" (Fig. 3). Taking Lead II first we see that there is a regular sequence of P-waves following one another at an interval of 1.56 to 1.59 sec. (corresponding to a rate of 38 per minute) and a regular sequence

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of ventricular complexes following one another at intervals of 1.50 to 1.56 sec. (rate: 38 to 40 per minute). There is a constant change of the position of the P-waves in relation to the ventricular complexes

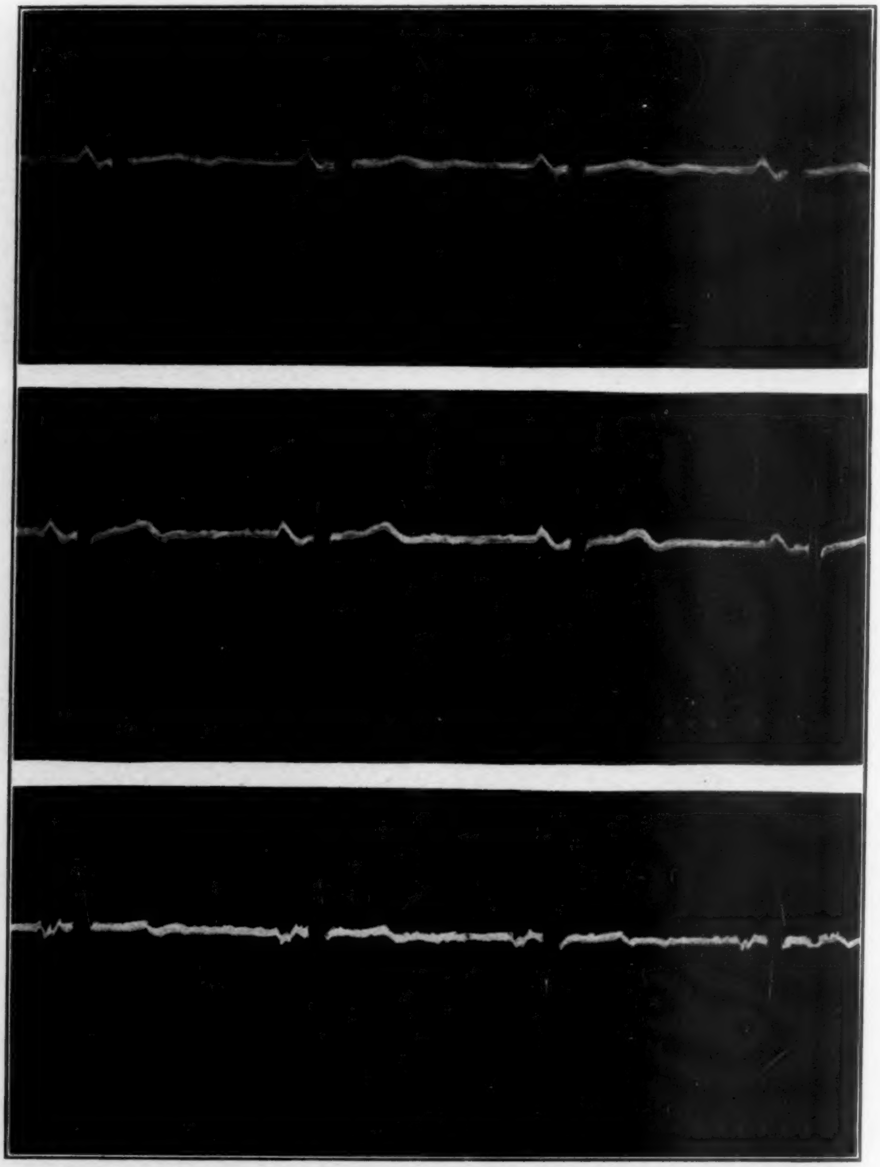

Fig. 1.—Electrocardiogram taken in 1925, showing sinus bradycardia. Leads I, II, and III. Time in tenths of a second.

indicating that these two rhythms are independent of one another. We are thus dealing with a case of dissociation of the action of the heart the auricles being stimulated by a center situated in—or in the

vicinity of—the sino-auricular node, and the ventricles following another pacemaker which must be situated above the site of division of the main bundle of His because of the normal shape of the ventricular complexes. It will also be noticed that the rate of the atrioventricular rhythm stimulating the ventricles is faster than the auricular rate. It is this difference in the rates of the two rhythms which causes a constant change of position of the P-wave in relation to the ventricular complexes. Leads I and III show the same phenomenon but demonstrate, moreover, that whenever an auricular impulse falls sufficiently late after a ventricular contraction so that it reaches the ventricles after their refractory period, it leads to a contraction of

Fig. 2.—Teleradiogram, taken Oct. 22, 1935.

the ventricles. Thus we see in Lead I that the first auricular contraction which occurs 0.22 sec. after the end of the preceding ventricular one is conducted to the ventricles and is followed by a ventricular complex after a P-R interval of 0.32 sec. The shape of the ventricular complex differs from those of the atrioventricular beats. This difference must be ascribed to aberrant conduction due to the fact that the conducting system had not completely recovered since the preceding beat, and therefore the conduction within the ventricles follows different paths. The phenomenon of aberrant conduction is well known in connection with early auricular extrasystoles (Lewis). The last ventricular beat in Lead I is another instance of the conduction of an

auricular impulse to the ventricles; here the auricular contraction occurred 0.24 sec. after the preceding ventricular complex and is conducted to the ventricles with a P-R interval of 0.32 sec. Lead III shows two conducted beats, the second and the fifth; in either case the auricular contraction follows the preceding ventricular one after 0.22 sec. and is conducted to the ventricles in 0.34 and 0.32 sec. respectively.

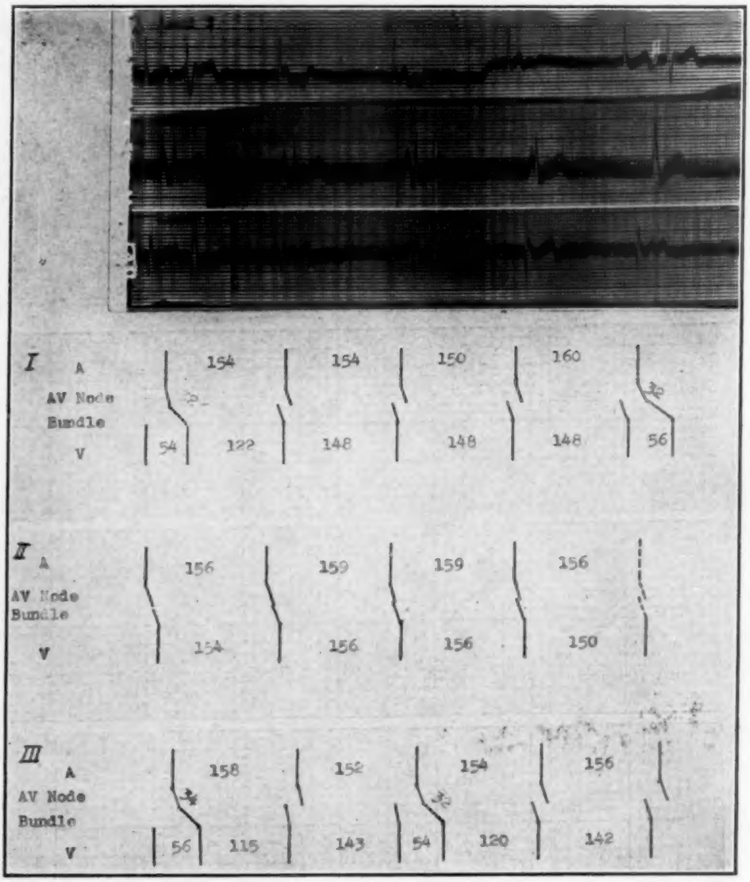

Fig. 3.—Electrocardiogram taken Oct. 22, 1935. Leads I, II, and III, showing dissociation with interference. For explanation see text and key below the tracing. Time in this and all the subsequent figures in twenty-fifths of a second.

This tracing shows therefore that the regular beats as found on auscultation are atrioventricular beats and that the "premature beats" which disturb the regular rhythm are due to the occasional conducted auricular beats.

One should expect the interval between a conducted impulse and the following atrioventricular impulse to be equal to the interval between two atrioventricular impulses, because the conducted impulse

when passing the atrioventricular center temporarily interferes with the impulse formation in the atrioventricular node, and therefore the impulse starts to form again in the atrioventricular center when the conducted impulse has left the center. In the present case, however, the time interval between the conducted beat and the following atrio-

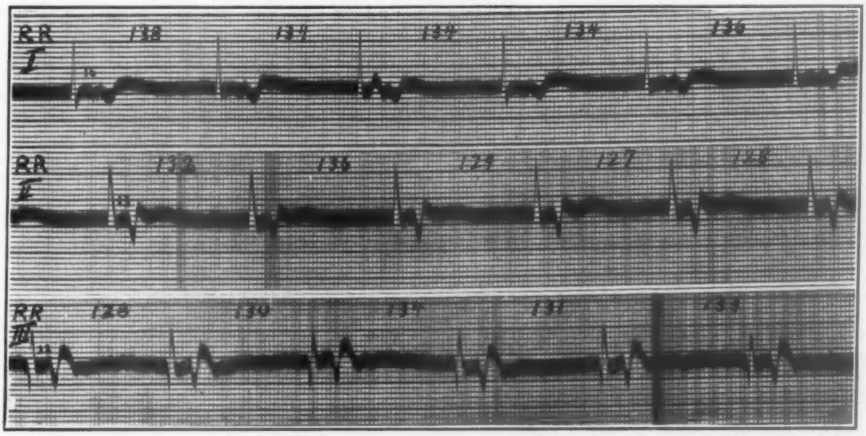

Fig. 4.—Electrocardiogram taken Oct. 24, 1935. Leads I, II, and III, showing atrioventricular rhythm.

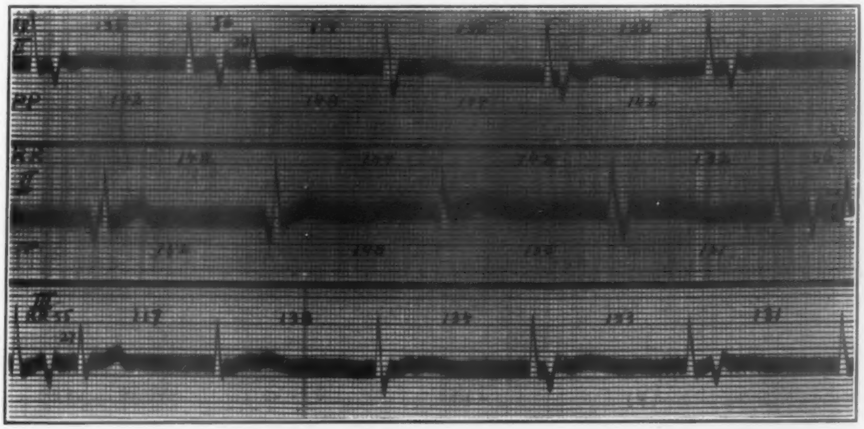

Fig. 5.—Electrocardiogram taken a few minutes after Fig. 4. Lead II only. Showing dissociation with interference and intra-auricular disturbances of conduction.

ventricular impulse is shorter than the time between two successive atrioventricular beats. Thus, in Lead I, the interval between the second—conducted—and the following—atrioventricular—beat is only 1.22 sec. as compared with the interval of 1.48 sec. separating the following atrioventricular beats. This phenomenon is of considerable theoretical importance and will be discussed later.

A coexistence of two independent rhythms, a sino-auricular and an atrioventricular one, can of course occur only when there is no retrograde conduction of the atrioventricular impulses to the auricles.

The patient came to see me again two days later and the first electrocardiogram taken on that occasion (Fig. 4) shows a different condition although no treatment had yet been inaugurated. In this tracing we see only an atrioventricular rhythm, the ventricular complexes following one another at a time interval of 1.27 to 1.36 sec. (rate: 44 to 47 beats per minute). Negative P-waves follow the ventricular complexes at an R-P interval of 0.16 to 0.18 sec. in Lead I, 0.11 to 0.13 sec. in Lead II and at a Q-P interval of 0.22 to 0.23 sec. in Lead III. We are dealing therefore with an atrioventricular rhythm originating in the lower parts of the A-V node, and the fundamental difference between this and the first electrocardiogram (Fig. 3) is that here every atrioventricular impulse is conducted backward to the auricles.

Atrioventricular rhythm is often a transitory phenomenon. The next tracing taken only a few minutes after the preceding one shows that the condition had changed again and that dissociation with interference had replaced the atrioventricular rhythm (Fig. 5). In this immediate succession. The similarity between this tracing and the tracing Lead II only was used, and the three strips were taken in first electrocardiogram (Fig. 3) is very striking, particularly with regard to the time relations. We see again the dissociation of the two rhythms: P-waves following one another at time intervals of 1.40 to 1.52 sec. and independently herefrom ventricular complexes following one another at intervals of 1.31 to about 1.48 sec., and again auricular impulses are conducted to the ventricles when they occur sufficiently late after the preceding ventricular contraction so as to reach the ventricles after their refractory period. Two features of this tracing call for special mention. The first is that the top tracing taken by itself could be interpreted as indicating an atrioventricular rhythm with gradually lengthening R-P intervals; if this interval exceeds a certain limit, the auricular contraction, itself inaugurated by the atrioventricular node, gives rise to a second ventricular contraction, the excitation wave which had traveled from the A-V node upward to the auricles, returning and stimulating the ventricles which are by then past their refractory period. This phenomenon has been described as "reciprocated beats" on several occasions (White, 1915, Gallavardin and Gravier; Drury). However, this explanation is untenable if one takes into consideration the middle tracing taken immediately after the top one. Here we see that in the two first beats negative P-waves precede the ventricular complexes, which fact makes it extremely improbable that we are dealing with an atrioventricular rhythm

originating in the lower parts of the A-V node. Moreover, the time relations as shown in this tracing and in Fig. 3, which is undoubtedly indicative of a dissociation with interference, give every reason to assume that we are dealing here as well with the coexistence of an auricular and an atrioventricular rhythm and that the two rhythms are occasionally linked up by conducted auricular beats. If this con-

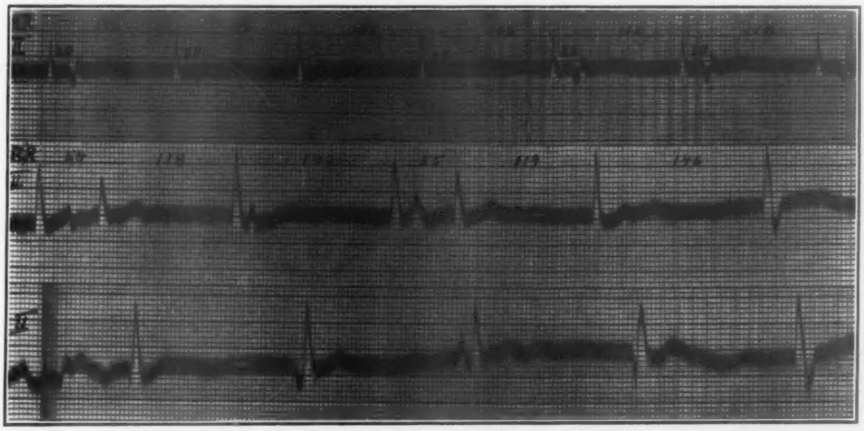

Fig. 6.—Electrocardiogram taken immediately after mild exercise test. Lead II only, top curve showing atrioventricular rhythm, middle curve showing dissociation with two conducted beats, bottom curve showing dissociation; intra-auricular disturbances of conduction in all three strips.

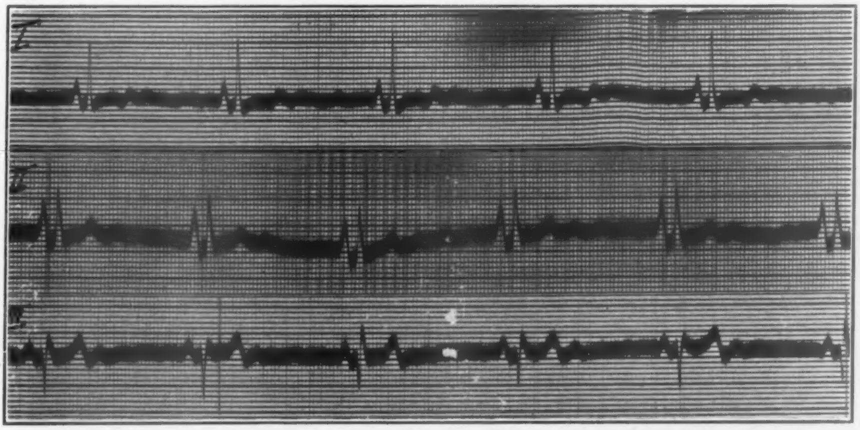

Fig. 7.—Electrocardiogram taken Oct. 30, 1935, after administration of small doses of digitalis. Leads I, II, and III. Showing sinus bradycardia.

ception is correct we have to account for the fact that here—in contradistinction to Lead II in Fig. 3—the P-waves are negative. The most reasonable explanation is that this is due to intra-auricular disturbances of conduction, and this conception receives support if one considers the result on the electrocardiogram of an exercise test, as shown in Fig. 6. All three strips represent Lead II, taken in immediate

succession. The top curve shows atrioventricular rhythm; the time intervals are shortened to 1.08 to 1.18 sec. as a result of exercise; the R-P interval is constant (0.20 sec.), but the P-waves differ in shape one from another: the site of impulse formation remaining the same, this can be due only to intra-auricular disturbances of conduction. The middle and bottom curves show that with the gradual slowing of the heart rate after the termination of the exercise test the two independent rhythms are reëstablished, but the bottom tracing shows by the varying shape of the P-waves that even then the intra-auricular disturbances of conduction persisted.

The patient was given small doses of digitalis and when I saw her again six days later sinus rhythm was restored, the electrocardiogram showing a sinus bradycardia with an average ventricular rate of 39 and a P-R interval of 0.20 sec. (Fig. 7).

DISCUSSION

One of the fundamental laws of the action of the heart is that the heart follows that pacemaker which forms impulses at the highest rate. Thus, as normally the sino-auricular node possesses the highest automaticity, the rhythm of the normal heart is the sinus rhythm. If, however, impulses originate at a higher rate in the atrioventricular node than in the sino-auricular node—this may occur as the result of either an abnormally great irritability of the atrioventricular node or of a depression of the normal impulse formation in the sino-auricular node—then the heart will follow the rhythm set up by the atrioventricular node. If there is no retrograde block, the excitation wave will spread to the auricles as well as to the ventricles, and the result is atrioventricular rhythm (Fig. 4). If, however, the spread of the excitation wave to the auricles is blocked ("reversed block"), then the auricles will be stimulated by the sino-auricular node (which, as the result of the block, is not reached by the impulses originating in the atrioventricular node) and the ventricles only will be stimulated by the atrioventricular impulses. In this condition there is therefore a dissociation of the cardiac mechanism present, characterized by the coexistence of a ventricular rhythm of a higher rate, originating in the atrioventricular node, and a sino-auricular rhythm of a lower rate, originating in the sino-auricular node. Most of the sino-auricular impulses will fail to yield a response from the ventricles because they reach the ventricles within their refractory period. However, as the rate of the impulse formation in the sino-auricular node in such a case is lower than that in the atrioventricular node, there will be a continuous shifting of the two rhythms, and those sino-auricular impulses which reach the ventricles outside their refractory period will

yield a ventricular contraction and at the same time, while traveling through the junctional tissues, will interfere with the formation of impulses in the atrioventricular node. The result is that with these conducted sino-auricular beats, and with these only, the two rhythms are linked with one another. The next atrioventricular beat following such a conducted sino-auricular beat usually occurs after a time interval corresponding to the rate of impulse formation in the atrioventricular node because the conducted impulse had temporarily disturbed the atrioventricular impulse center. This interval, however, may be shortened for reasons discussed below in connection with the present case.

Such a condition characterized by the coexistence of a faster atrioventricular and a slower sino-auricular rhythm with occasional interference of the slower with the faster rhythm has been originally described by Wilson and by White; it has become more universally recognized as an arrhythmia sui generis by the extensive studies of Mobitz, who called this condition "Interferenzdissoziation." In English one might call it dissociation with interference, in analogy to Wenckebach's terminology, *Dissoziation mit Interferenz.*

On ordinary clinical examination this condition is bound to be mistaken for a case of normal sinus rhythm with occasional extrasystoles. Auscultation reveals a regular somewhat slow rhythm with occasional premature beats. It will be clear from the foregoing analysis, however, that the regular rhythm is in reality the atrioventricular rhythm and that the premature beats are not ectopic beats, but the conducted sino-auricular beats.

The present case presents several individual features of interest. As to the underlying mechanism, we know in this case that for the last eleven years at least there was a sinus bradycardia, as verified by electrocardiograms, so that we have every reason to assume that there has been for years an interference with the normal impulse formation in the sino-auricular node. The cause of the temporarily increased activity of the atrioventricular node remains unknown, however. Second, from a clinical point of view, it is important to note that small doses of digitalis lead to a symptomatic cure. The only complaints of the patient were "palpitations," and these were caused by the arrhythmia produced by the "interfering" conducted auricular impulses. The effect of digitalis in this case was to depress the impulse formation in the atrioventricular node so that its automaticity became again less than that of the sino-auricular node, with the result that sinus bradycardia of a rate of about 38 was restored. With the abolition of the arrhythmia the palpitations disappeared, and the patient lost the discomfort. This effect of *small* doses of digitalis is the more

remarkable, as in many of the previously described cases exhibiting this type of arrhythmia the condition had been *caused* by *large* doses of digitalis.

It is worth noting that a mild exercise test (10 times sitting up) caused the rate to increase to 42, sinus rhythm persisting.

From a physiological point of view the fact mentioned above, that the interval following a conducted auricular impulse was shorter than the interval between two atrioventricular beats, calls for special explanation. This phenomenon was first described by Scherf, and the explanation given for his case seems not only to be the adequate one for this case, but also to receive additional support by it. If the conducted impulse traveling through the junctional tissues temporarily interferes with the impulse formation in the atrioventricular node, the impulse formation in the atrioventricular node begins again at a moment when the conducted impulse has left the A-V node. This moment practically coincides in most cases with the moment in which the activation of the ventricles starts, as indicated in the electrocardiogram by the onset of the ventricular complex, because the conduction of the impulse through the bundle of His and the lower parts of the junctional tissues is fast. Therefore the interval between the conducted beat and the following atrioventricular beat is approximately equal to the interval between two atrioventricular beats. For those cases, however, in which the interval after the conducted beat is materially shortened, Scherf assumes a disturbance of, and delay in, conduction of the excitation wave of the conducted beat through the bundle of His. The result of this delay is that an abnormally long interval elapses between the moment when the excitation wave of the conducted beat leaves the atrioventricular node and when it activates the ventricles. The formation of the next atrioventricular impulse however starts when the excitation wave of the conducted beat has left the atrioventricular impulse center. By the time this atrioventricular impulse travels through the bundle, the junctional tissues have had sufficient time to recover, and this next excitation wave reaches the ventricles in the normal time, thus leading to the shortening of the interval following the conducted beat. Scherf gives good reasons for this assumption, and the present case exhibits features which may be quoted as additional support: viz., electrocardiographic evidence of disturbances of conduction of various kinds: the conducted beats show a lengthening of the P-R interval to as much as 0.32 sec. as against 0.20 sec. during sinus bradycardia; the ventricular complexes of the conducted beats have a different shape from the atrioventricular ones due to aberrant conduction; and last, there are the differences in the shape of the P-waves indicative of intra-auricular disturbances of conduction.

SUMMARY

A case of dissociation with interference of the heart is described and the underlying mechanism of the arrhythmia is discussed.

The special features of the case are:

For the last eleven years at least sinus bradycardia was present, as shown by the history and verified by electrocardiograms.

There was electrocardiographic evidence of disturbances of conduction both in the bundle of His and in the auricles.

Atrioventricular rhythm occurred at times, the impulses originating in the lower parts of the atrioventricular node, stimulating the auricles as well as the ventricles.

Small doses of digitalis effected a symptomatic cure.

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THE ELECTROCARDIOGRAM DURING AND AFTER EMERGENCE FROM DIABETIC COMA*

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ALTHOUGH both clinical and necropsy observations suggest that the heart is severely deranged in diabetic coma, electrocardiographic evidence of such derangement has not been frequently or consistently found. Previous studies of the electrocardiographic changes that develop during severe diabetic acidosis have led to somewhat inconsistent and contradictory conclusions. Certain observations suggested to us that rather marked and, on the whole, consistent alterations of the T-waves and lengthening of the Q-T interval were present during certain stages of diabetic coma, not as one might expect at the height of the coma, but rather after the acidosis had been partially or even completely controlled. These observations led us to study the matter carefully in a series of seventeen cases of diabetic coma and six cases of "precoma," the result of which is the subject of this report.

LITERATURE

Hepburn and Graham[7] in 1928 made electrocardiographic studies in 123 cases of diabetes mellitus and concluded that none of the patients with severe acidosis showed an abnormal electrocardiogram. Taterka[15] in 1929, studying cases of diabetic coma, observed extrasystoles and a diminution in the amplitude of all deflections; the changes affected particularly the T-waves, which were either depressed or entirely negative. This author felt that the condition of the heart before the onset of coma was an important factor in the production of these changes and that these changes were more marked the longer the duration of the coma and the greater its severity. Unfortunately the published paper includes no electrocardiographic records. Smith and Hickling[13] studied electrocardiographically a group of 20 patients, all of whom had severe diabetes with varying degrees of ketosis but without actual or impending coma. Tracings were taken before treatment was begun and at intervals of from two to seven days thereafter. Of these 20 individuals, 2 showed inverted T-waves in Lead I; and 2, inverted T-waves in Lead II; in all 4 instances these waves became upright after treatment. Alterations of the T-waves of Lead III, more or less marked, occurred in 11 of the 20 patients. Faulkner and Hamil-

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ton[4] were of the opinion that there were no published data to indicate that the degree of acidosis reached in disease is sufficient to cause profound electrocardiographic disturbances. These authors made electrocardiographic studies of 15 cases of diabetic coma, the procedure being to take an electrocardiogram immediately on admission in coma and a control record from one to eight days later. They found the electrocardiogram to be within normal limits in 9 cases, while in 4 the only abnormal features (diaphasic T_1 or T_2 or both) might be explained by overshooting, due to high skin resistance. Only two patients showed minor T-wave changes which could not be explained in this manner. They concluded that "electrocardiographic changes are not the rule in diabetic coma and when present they consist of minor abnormalities which are not likely to be confused with or to mask the picture of coronary occlusion." As far as we are aware, Klingenberg[8] is the only author who has felt that there were consistent electrocardiographic changes during and following severe diabetic acidosis. He observed normal electrocardiograms in only one of ten patients in diabetic coma.

METHODS

The 17 patients of our series were studied electrocardiographically as soon as feasible after their admission to the hospital. In thirteen cases the first electrocardiogram was taken within one to six hours after admission in coma; in 2, within six to twelve hours; in 3, between twelve and twenty-four hours; and in one case, thirty-eight hours after admission. The first electrocardiogram in two-thirds of the cases was therefore taken within a comparatively short time after admission while the patient was still in a state of acidosis, but, in almost all instances, not before the patient had received varying amounts of insulin, glucose, and fluids. Tracings were made every day at 10:00 A.M. and 4:00 P.M. as long as electrocardiographic changes were present (usually for from four to six days) to determine whether certain changes might be present in the postacidotic period as well as during coma. During the remainder of the stay in the hospital, usually for more than a month, tracings were taken once a day.

MATERIAL

Seventeen patients in diabetic coma and 6 in precoma were studied in the manner discussed above; 2 of the 17 were studied during two periods of coma. The series was not at all selected, the cases included representing successive admissions to the hospital. All of these showed the well-known clinical picture: subnormal temperature, rapid pulse, Kussmaul respiration, moderate or marked hyperglycemia, with ketosis and a plasma carbon dioxide combining power of the blood of 20 volumes per cent or less. In 9 of the 17 cases the coma during and following which we made our studies constituted the first recognized

TABLE I

CHEMICAL DATA

NO.	NAME	DATE OF ADMISSION	AGE	COLOR	SEX	HR. IN ACIDOSIS BEFORE ADMISSION (ESTIMATED)	HR. IN ACIDOSIS AFTER TREATMENT STARTED	ADMISSION BLOOD SUGAR (MG./100 C.C.)	ADMISSION (CO_2 VOL. %)	ADMISSION UREA N (MG. 100 C.C.)	ADMISSION PLASMA CHLORIDES (MG. 100 C.C.)	TOTAL UNITS INSULIN ADM. DURING ACIDOSIS	TOTAL FLUID AS N. S. S. (C.C.)	TOTAL SODIUM BICARB. (GM.)	TOTAL GLUCOSE (GM.)	COMPLICATIONS
1	M. B.	8/26/35	35	W	F	5	10	864	20	17	524	316	3000	0	65	Enteritis
2	W. B.	6/ 5/35	43	B	F	24	14	300	16	16	608	145	6500	36	275	Carbuncle
3	E. B.	5/24/35	24	W	M	24	19	816	14	48	492	205	7100	5	104	None
4	J. B.	1/ 6/35	20	W	M	48	3	904	15	30	474*	120	3000	8	30	None
5	F. C.	1/20/35	39	B	F	8	12	1024	15	63	—	430	4450	29	50	None
6	B. C.	6/18/35	42	**B**	**F**	**96**	**6**	**992**	19	38	508	130	4500	30	30	None
7	C. C.	1/30/35	16	B	F	30	10	680	13	19	524	280	3170	32	110	None
7a	C. C.	9/ 6/35	16	B	F	96	20	352	14	11	615	430	3650	14	210	None
8	N. D.	12/23/34	21	B	F	48	10	1850	13	95	430*	660	5000	30	90	Pneumonia
9	C. D.	3/29/35	42	W	F	48	7	612	12	35	—	180	4900	32	120	None
10	E. F.	12/10/34	57	W	M	12	9	756	13	12	434*	270	2600	13	230	None
11	J. G.	7/27/35	20	B	M	24	8	808	12	30	526	250	3000	43	90	None
11a	J. G.	5/ 6/35	20	B	M	24	8	800	14	35	468	90	2500	32	60	None
12	L. J.	9/ 6/35	48	B	F	24	64	848	11	21	568	490	4500	—	215	None
13	J. P.	3/20/35	22	B	M	60	8	1056	14	43	—	220	5000	43	90	None
14	G. R.	3/20/35	31	W	F	24	15	548	17	14	534	230	5400	32	180	None
15	B. R.	2/ 1/35	61	B	F	8	11	736	18	30	564	335	4800	30	160	Sepsis
16	M. W.	9/ 9/35	46	W	F	48	54	912	11	34	—	490	4250	—	125	None
17	F. Y.	2/ 5/35	38	B	F	8	7	708	12	15	554	240	3800	30	120	None

*Whole blood chloride.

evidence of diabetes. In the remaining patients, all of whom were known to be diabetic, coma in each instance resulted from failure to follow the advised dietary and insulin program. In addition to the 17 cases, we also studied in a similar manner 7 cases of precoma. Although the data obtained in the precoma cases are not included in our tables, a brief summary of the findings in this group is included in the results of this study.

Complications.—Complications were unusually infrequent in our series of cases. One patient (Case 2) developed post-coma lobar pneumonia, from which she made an uneventful recovery, and another (Case 6) died fifty-four days after admission from dermatitis gangrenosa and a severe urinary tract infection.

Age, Sex, and Race.—Twelve of our 17 patients were females and 5 were males. Ten were white, and 7 were colored. The ages ranged from seventeen to sixty-one years, the average of the entire group being thirty-five years. According to age groups, they can be arranged as follows:

10-20 yr.	21-30 yr.	31-40 yr.	41-50 yr.	51-60 yr.	61-70 yr.
3	3	4	5	1	1

Cardiovascular Status.—The estimate of the cardiac and circulatory systems was arrived at by examining the patients after their acidosis had been alleviated. The clinical and graphic studies made at the time of discharge led us to conclude that the heart, blood pressure and arterial systems were within normal limits in 14 of the 17 cases. In one of the remaining 3 cases, clinical examination revealed no evidence of disease, but inverted T-waves were present in Leads II and III of the electrocardiogram. In a second case the heart was not abnormal, but the patient showed a rather pronounced generalized arteriosclerosis. In the third instance there was a slight cardiac enlargement; a soft, systolic murmur was audible at the apex; and the blood pressure was 154/96 at the time of discharge from the hospital. No drugs belonging to the digitalis group were administered during the period of our observation except strophanthin, gr. $\frac{1}{100}$, given intravenously in two divided doses in Case 6.

Treatment.—All our patients received routine chemical studies consisting of the frequent determination of the blood sugar, the carbon dioxide combining power of the plasma, the urea nitrogen concentration of the blood, and the plasma chloride values. The routine treatment of diabetic coma was applied to all cases of our series. Insulin, in total amounts from 90 to 661 units, the average being 311, was administered during the period of acidosis. Fluids in the form of normal saline solution were always given either subcutaneously or intravenously in average total amounts of 4,186 c.c. during the period of acidosis. Glucose was given freely, orally, subcutaneously, or intravenously in average total amounts of 126 gm. Sodium bicarbonate

was administered through a retained gastric tube in quantities varying from 5 to 43 gm. during the period of acidosis in all except Cases 1, 12, 14, 15, and 17. Acacia was given intravenously in Case 8. When the carbon dioxide combining power had risen to 45 volumes per cent, the patient was considered to have recovered from acidosis.

ELECTROCARDIOGRAPHIC CHANGES

Electrocardiographic changes, more or less marked, were observed in all the seventeen cases of our series; in the second admission for coma of Case 7 the alterations were insignificant. Although there were slight alterations in the P-waves, the P-R intervals, and the QRS complexes, these were of minor importance. The striking changes that we wish to emphasize were observed in the T-wave and the Q-T interval. The T-wave changes were remarkable for their consistency, so much so that in typical cases they might be regarded as almost characteristic. The abnormalities were transient, usually reaching their maximum development not during coma but after coma. The changes disappeared in all but one instance. In Case 3 inverted T-waves in Leads II and III, although undergoing changes in form, tended to persist. Unfortunately we have no control electrocardiogram before the onset of coma in this case. The time interval from admission in diabetic coma to complete return to normal varied from three to ten days, the average being five days. In seven cases of this series electrocardiographic changes were again observed after the electrocardiogram had initially returned to normal, the changes being quite marked in three of these. The electrocardiograms of the patients in this group ultimately returned to normal except in Case 6, in which the electrocardiogram, having returned to normal after the acidosis had been controlled, later presented marked T-wave changes so that the electrocardiogram at discharge could not be considered normal. In the cases just referred to, in which the electrocardiograms after initial return to normal varied on successive days, the tracings taken in the afternoon showed marked improvement over those taken in the morning. We are not able, definitely, to explain this finding. In nine cases sudden electrocardiographic changes were observed to appear in a comparatively short period of time. In two cases (Cases 14 and 15) marked changes were observed in the space of two hours.

Some difficulty in taking an electrocardiogram was occasionally experienced by reason of the high skin resistance presented by the patients in coma. However, by the use of salt, pumice, and tragacanth paste and by brisk and repeated rubbing, we were able to obtain tracings which on the whole were quite satisfactory.

The high rate in the initial electrocardiogram (120 to 150 per minute) at times rendered the accurate determination of the Q-T intervals difficult.

The alterations which were noted will now be presented in detail.

T-Waves.—The T-wave changes in diabetic coma and upon emergence from this state were remarkable, not only for the presence of marked deviations from the normal, but for the completeness with which these altered waves returned to normal. In many instances the T-waves upon admission in diabetic coma showed little change from the normal

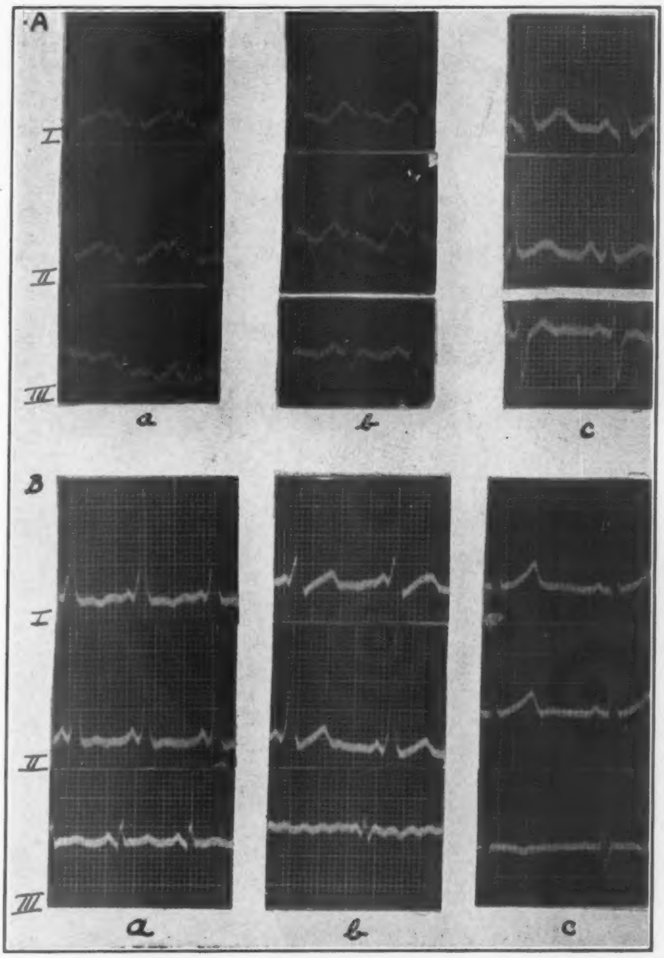

Fig. 1.—*A* (Case 15): *a*, tracing made at 9 P.M., Feb. 1, 1935, two hours and twenty minutes after admission in coma, shows slight tachycardia and upright T_1 and T_2 of somewhat diminished amplitude; *b*, tracing made Feb. 2, 1935, at 9:48 A.M., thirteen hours after *a*, when the patient was out of acidosis and clinically better, shows inverted T_1 and T_2 and a long Q-T interval; *c*, tracing made Feb. 5, 1935, four days after admission in coma. This tracing is now practically normal.

B (Case 11a): *a*, tracing made May 6, 1935, at 12 M., ten hours after admission in coma—patient had been out of acidosis for two hours. Note inverted T_1, low amplitude T_2, short P-R interval and prolonged, slurred QRS complexes. *b*, Tracing made May 7, 1935, at 2:50 P.M. Note that T_1 and T_2 are now upright but that the P-R intervals are still short and the QRS complexes prolonged. *c*, Tracing made May 31, 1935, at 10 A.M., normal.

(Fig. 1); subsequent electrocardiograms taken twenty-four hours after admission showed marked T-wave alterations, the T-wave becoming

either inverted or the S-T interval being markedly depressed, and usually being associated with prolongation of the Q-T interval. A gradual return of the T-wave to normal occurred in most cases. A rather sudden return was observed in others. The following types of changes were noted: elevation of the S-T interval (2 cases); inverted, changing to depressed T-waves (3 cases); low amplitude (2 cases); in another case they were unchanged. The most frequent change observed was depression of the S-T interval accompanied by an alteration in the T-wave (Fig. 2*Aa*, and Fig. 3*b*). This T-wave change might be regarded as almost typical. This depression is not unlike that observed as the result of the action of digitalis, with the notable difference that in these cases the S-T interval is prolonged, whereas in the T-wave produced by digitalis it is shortened.[3] In the few cases

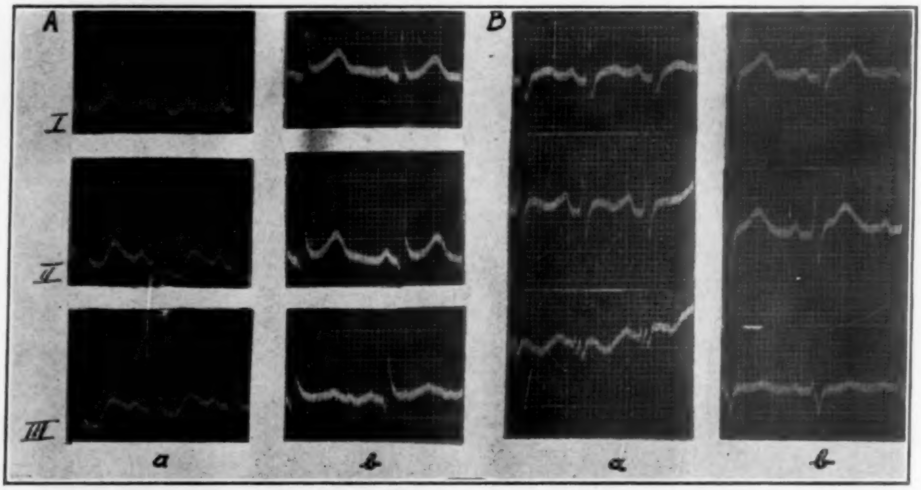

Fig. 2.—*A* (Case 5): *a*, tracing made Jan. 21, 1935, at 11:55 A.M. (twenty-five hours after admission in coma); patient had been out of acidosis for nineteen hours. S-$T_{1,2,3}$ are depressed. The Q-T interval is prolonged. *b*, Tracing made Jan. 22, 1935, at 11:10 A.M., twenty-four hours later. Note that this electrocardiogram is now practically normal.

B (Case 7): *a*, tracing made Jan. 31, 1935, at 5 P.M., (twenty-three hours after admission in coma); patient had been out of acidosis for thirteen hours. Note low amplitude of T_1 and inverted T_2 and T_3. *b*, Tracing made Feb. 1, 1935, at 3:15 P.M., is now practically normal.

in which the Q-T interval was not prolonged, the S-T depression was practically indistinguishable from stage 2 or 3 of a digitalis S-T depression.[10] These changes were most marked in Leads II and III although all three leads were not infrequently involved. The changes in Lead III, however, were frequent and characteristic. When a reversion to normal occurred, Lead I was the first to show this change and Lead II followed.

Q-T Intervals.—The Q-T interval has been used as a measure of electrical ventricular systole.[2] White and Mudd[16] found the Q-T intervals to be prolonged in bundle-branch block, in the presence of low blood

serum calcium, in ventricular paroxysmal tachycardia and in auricular paroxysmal tachycardia. Von Haynal[5] and Schaffer, Bucka and Friedlander[12] observed lengthening of this interval following the administration of insulin. Lengthening of the Q-T interval was a

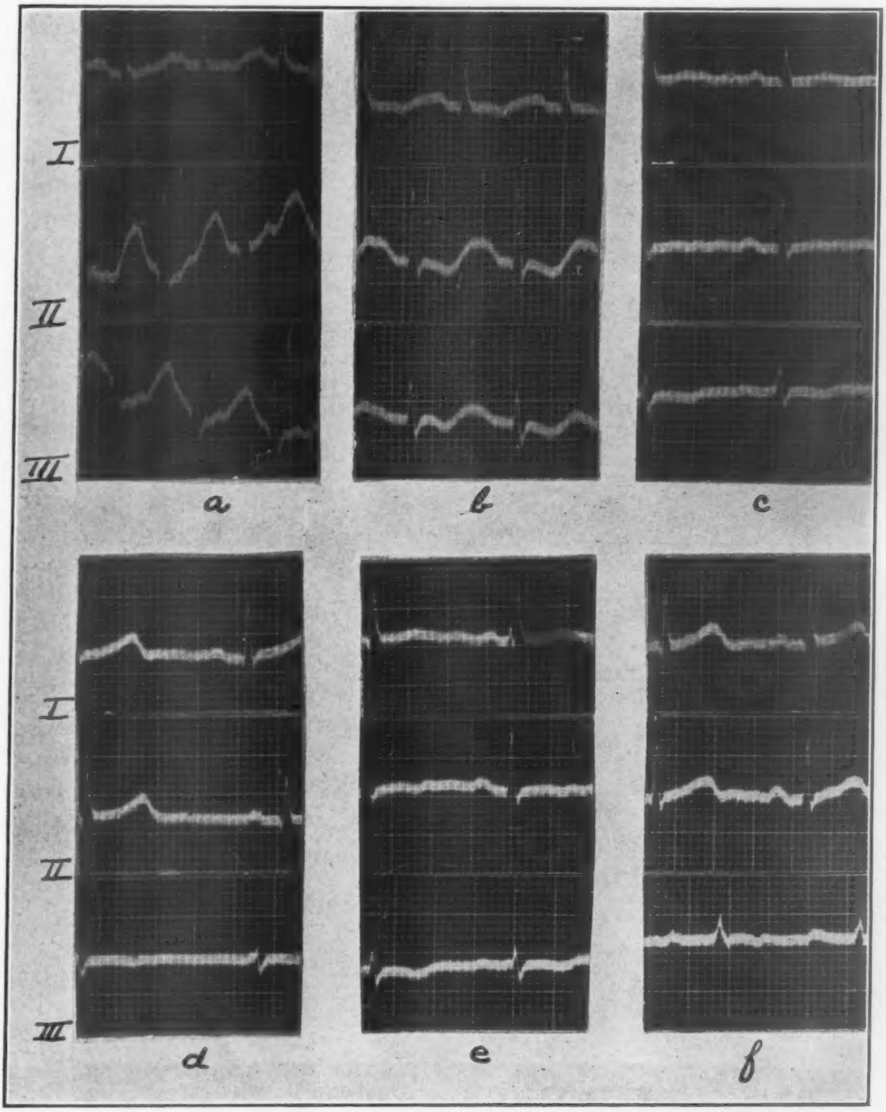

Fig. 3.—(Case 14): *a*, tracing made March 20, 1935, at 3:55 P.M., two hours after admission, patient in coma. Note S-T interval depression in Lead I, rather bizarre T_2 and T_3 and a long Q-T interval. *b*, Tracing made March 21, 1935, at 5:25 P.M., patient had been out of acidosis for 10.5 hours. T_1, T_2 and T_3 are inverted; the Q-T interval is prolonged. Subsequent tracings showed gradual improvement with return to normal. *c*, Tracing made March 27, 1935, at 9:45 A.M. The T-waves in Leads I and II are now upright but of low amplitude; T_2 is flattened. *d*, Tracing made March 27, 1935, at 4:10 P.M. shows T_1 and T_2 upright and of normal amplitude. Normal tracing. *e*, Tracing made March 28, 1935, 10:38 A.M., 18.5 hours after *d*, again shows a tracing similar to *c*. *f*, Tracing made March 28, 1935, 4:05 P.M., 5.5 hours after *e*, is again normal.

prominent finding in the cases of diabetic coma that we studied. According to the formula of Bazett,*[1] $S = K \sqrt{C}$ as a measure of the normal Q-T interval, our results indicated that it was prolonged from 20 to 50 per cent above its normal value in thirteen of our seventeen cases. In Case 3, this finding constituted the only definite electrocardiographic change observed. Its presence is often difficult to determine clearly in the initial electrocardiogram because of the high ventricular rate. The change was observed not only during actual coma, but it usually persisted for from three to five days after the acidosis had been effectively controlled. The return to normal was usually gradual, but at other times it was quite abrupt, a prolonged interval returning to normal (Case 15) in a space of six hours. The prolongation of the Q-T interval was present for one or two days in thirteen of our seventeen cases.

P-Waves and P-R Intervals.—The P-waves were normal in all but three cases. Of these one showed an extremely tall P-wave on the day after admission; another showed a bifid P-wave on the third day after admission; a third showed on the day of admission auricular flutter which gave way to a normal rhythm in twelve hours.

The P-R intervals were normal except in 2 cases; in one (Case 7a) the P-R interval was prolonged to 0.22 sec. on the third day after admission; in the other (Case 11 and 11a) there was a short P-R interval (0.06 sec.) with a prolonged QRS complex, which abnormality lasted six and seven days on the first and second admissions, respectively (Fig. 1, *B*).

QRS Complexes.—The QRS complexes were normal in all but 3 cases. In one (Case 3), as the patient emerged from coma, an initial low amplitude of R_1 changed to a higher amplitude in tracings taken from four to six days after emergence from coma. Slight slurring of the QRS complexes was observed on the second day in Case 13. The presence of short P-R intervals with prolonged QRS complexes for six and seven days, respectively, in the same patient on two different admissions in coma (Case 11) has been discussed under P-R interval changes.

Arrhythmias.—A normal sinus rhythm was present in all cases except for the presence of a transient auricular flutter in one patient (Case 10). In another patient, ventricular extrasystoles were observed on the third day after emergence from the coma (Case 13), and auricular extrasystoles were observed on the first day in a third case (Case 17).

Relation of Maximum Electrocardiographic Changes to Acidotic State.—Although the electrocardiographic studies in thirteen cases were made from two to six hours after admission in coma, the most marked electrocardiographic changes were observed, not in the first electrocardiogram while the patient was still in coma, but at a slightly later

*In this formula S = length of systole; K = a constant; C = cycle length.

TABLE II

ELECTROCARDIOGRAPHIC FINDINGS

CASE NUMBER	RATE PER MINUTE IN INITIAL EKG.	INTERVAL BETWEEN ADM. & INITIAL EKG. (IN HR.)	DURATION OF ACIDOSIS AFTER ADMISSION (IN HR.)	INTERVAL BETWEEN ADM. & MOST ABNORMAL EKG. (IN HR.)	INTERVAL BETWEEN ADM. & RETURN TO NORMAL EKG. (IN DAYS)	IMPORTANT ELECTROCARDIOGRAPHIC CHANGES
1	120	6	10	29	8	Elevated S-T intervals in Leads II and III; Q-T interval, not prolonged.
2	107	38	4	38	7	Depressed S-$T_{1,2}$; Q-T interval, normal.
3	100	4	19	22	6	Q-T interval, prolonged 3 days; bifid $T_{1,2}$; inverted T_2 became upright on 13th day and again inverted on 14th day after admission.
4	125	23	3	23	3	Inverted T_1; depressed S-$T_{2,3}$; the ekg. became practically normal within 24 hours; Q-T interval, prolonged 2 days.
5	115	25	12	25	3	Depressed S-T in all leads; within 24 hr. ekg. became practically normal; Q-T interval, prolonged 1 day.
6	140	2	6	35	6	After initial depression of S-T intervals, $T_{1,2}$ became deeply inverted; Q-T interval, prolonged for 1 day.
7	142	2	10	24	2	Ekg., normal during acidosis; T_1 low and $T_{2,3}$ inverted, 24 hr. later (alteration present only 24 hr.); Q-T interval, prolonged 2 days.
7a	120	7	20			No ekg. changes during second admission.
8	140	21	10	21	10	Depressed S-$T_{2,3}$; Q-T interval, prolonged 3 days.
9	140	2	7	23	7	Depressed S-T, all leads; after initial return to normal, T-waves were higher in P.M. than in A.M. on several successive days (see text); Q-T interval, prolonged 2 days.
10	140	3.5	9	8.5	3	Transient auricular flutter; depressed S-$T_{2,3}$; Q-T, prolonged 3 days.
11	140	4	8	24	6	Ekg., entirely normal during acidosis; 24 hr. later, P-R became short and QRS widened; these changes continued 6 days; Q-T, not affected.
11a	120	10	8	12	7	Short P-R with widened QRS, present in first ekg. and continued for 7 days; $T_{1,2}$ upright in 1st ekg. and inverted 2 hr. later, without changes in QRS; Q-T interval, not prolonged.
12	120	1.5	64	2	4	Elevated S-$T_{1,2}$; bifid $T_{1,2}$; Q-T, prolonged 4 days.
13	125	3	8	3.18	3	Depressed S-T intervals in all leads; ventricular extrasystoles on 3rd day; Q-T interval, prolonged 2 days; after initial return to normal, frequent transient T-wave varieties.

TABLE II—CONT'D

CASE NUMBER	RATE PER MINUTE IN INITIAL EKG.	INTERVAL BETWEEN ADM. & INITIAL EKG. (IN HR.)	DURATION OF ACIDOSIS AFTER ADMISSION (IN HR.)	INTERVAL BETWEEN ADM. & MOST ABNORMAL EKG. (IN HR.)	INTERVAL BETWEEN ADM. & RETURN TO NORMAL EKG. (IN DAYS)	IMPORTANT ELECTROCARDIOGRAPHIC CHANGES
14	150	2	15	16	7	Inverted T-wave and depressed S-T intervals in all leads; Q-T interval, prolonged 4 days; after initial return to normal T-waves were frequently taller in P.M. than in A.M. (see text).
15	125	2	11	13	4	Inverted T-waves and depressed S-T intervals in all leads; Q-T interval, prolonged 2 days; transient alterations of T-waves after initial return to normal.
16	120	1.5	54	20		Depressed $S\text{-}T_{1,2}$; this transiently reappeared after initial return to normal; Q-T intervals, not lengthened.
17	110	1	7	17	7	Depressed $S\text{-}T_{1,2}$; after initial return to normal, this reappeared transiently; Q-T prolonged for 4 days.

period when the patient was usually out of acidosis and appeared clinically improved. The most abnormal electrocardiogram in these thirteen cases was observed about twenty-four hours after admission. Of the remaining cases of the series, in Case 11a, the most abnormal electrocardiogram was observed twelve hours after admission, the first electrocardiogram having been taken two hours previously. Of the remaining four cases the most abnormal electrocardiogram was taken twenty-one to thirty-eight hours after admission. Thereafter the electrocardiogram tended to return gradually to normal. After a return to normal had taken place, other changes which will be discussed subsequently were observed.

The electrocardiograms of seven cases of precoma were studied in a manner similar to the cases of coma. In one of these cases the administration of digitalis complicated the electrocardiographic picture so that the results in six cases will be briefly recorded. The electrocardiographic changes were in every way similar, although slightly less marked than those observed in the case of patients in diabetic coma. Marked changes were observed in one case, moderate changes in four, and slight changes in one case. The Q-T interval was prolonged in every case; in one patient (Case 6P) the prolongation lasted eleven days, which was a longer period than in any other case of the entire series. The S-T interval was depressed in 5 cases and the

T-wave inverted in one case. In one case (4P) the T-waves were inverted in Leads I, II, and III and after a month had not yet returned to normal.

The explanation for the presence of the most marked electrocardiographic changes approximately twenty-four hours after admission is not entirely clear. It has been stated by Master and his associates[9] that in pneumonia the most abnormal electrocardiographic changes were obtained during the period of convalescence. It is quite possible that the maximum amount of myocardial derangement occurs many hours after inception of the acidosis. A parallel might be drawn with coronary occlusion in which the cardiac damage and the electrocardiographic findings may be most marked from twenty-four to forty-eight hours after the occlusion. The suddenness and completeness of return to normal in these cases, sometimes in the space of a comparatively few hours, is an incident the like of which we are not acquainted with in other cardiac states.

That the severity of the electrocardiographic changes is independent of the condition of the heart before the coma is indicated by the fact that the electrocardiographic changes were as frequent and as severe in the younger patients, in whom the hearts were apparently normal, as in the older diabetics with myocardial disease.

DISCUSSION

The marked electrocardiographic changes that we have described can be only the result of myocardial derangement. The striking feature of the alterations is their usual brief and transient nature. This would suggest that the myocardium is not permanently changed: that the effects are upon function rather than upon structure, as a rule. However, the changes are not always transient and reversible. This is indicated by Case 4P, in which the electrocardiogram continued to be abnormal for at least one month after the acidotic state had been completely controlled and also by the fact that the myocardium of individuals dying during diabetic coma is often markedly degenerated at necropsy.

This behavior suggests that the altered metabolic processes incident to diabetic coma, although usually affecting the function of the myocardium and therefore being reversible,* may, if they are long continued or very severe or if the muscle is for some reason particularly susceptible, alter the structure of the myocardium permanently and severely.

However, when an attempt is made to determine the factor or factors present during diabetic coma that are specifically responsible for the alteration of the myocardium, one is faced with a very complex

*The terms "reversible changes" and "irreversible changes" and their relation to functional and organic changes have recently been discussed by Bentley and Cowdry.[2]

problem, for many chemical and metabolic processes both intracellular and extracellular are profoundly altered during this state. Among the factors which may affect the myocardium are (1) acidosis per se, (2) the disturbances in electrolytes, especially sodium chloride, (3) alteration in the circulating blood volume, (4) dehydration, (5) the presence of azotemia, and finally (6) the effects of the various therapeutic procedures. Of these, insulin is perhaps most important, although the administration of normal saline, glucose, and sodium bicarbonate should also be considered. We have no personal observations nor have we found in the literature any evidence to commit definitely one of these factors as responsible for the alterations in the electrocardiogram. Any discussion on the possible rôle of these factors would therefore be largely hypothetical. We do, however, wish to consider briefly the possible rôle of insulin, for the reason that we have some data which indicate that it itself is not causative of the changes observed.

Insulin was administered in most cases in large doses during coma, often 50 to 100 units having been given before the first electrocardiogram was taken. That insulin can produce electrocardiographic changes coincident with the production of hypoglycemia is well established.[5, 11, 12, 14] Studies by Schaffer, Bucka, and Friedlander[12] von Haynal, Vidovsky, and Györgi,[6] and Soskin, Katz, Strouse, and Rubinfeld[14] have been reported in which the administration of insulin immediately covered by sufficient glucose to prevent hypoglycemia in a patient with cardiovascular disease also resulted in electrocardiographic changes. These alterations have been ascribed by these workers to the direct effect of insulin upon the myocardium. In spite of the conclusions of these authors, there are several reasons that lead us to feel that the changes observed by us, which were more marked and of a different character, cannot be attributed to the action of insulin per se. In the first place, in some of our patients, as in the series of Taterka,[15] profound alterations were observed in the electrocardiogram taken soon after admission in coma before the insulin administered could have produced any profound effects. In the second place, in many cases larger doses of insulin given after the return of the electrocardiogram to normal failed to produce consistently the changes noted during the acidotic state. The third reason we believe that insulin was not the cause of the alterations lies in the fact that we encountered the identical changes in a patient whose acidosis was nondiabetic in origin and who received no insulin whatever.

This patient, a colored woman aged thirty-two years, was admitted in ketosis on four separate times within the space of one year. Although she had a severe acidosis on each admission with the carbon dioxide combining power of the plasma below 20 volumes per cent, the blood sugar always ranged between 80 and 120 mg. per cent. While the cause of her acidosis has at this date not been finally deter-

mined, it is definitely not of diabetic origin. Insulin was administered during the first admission but not in the other three. The electrocardiogram of this patient (when insulin was not given), nevertheless, showed findings similar to those above described, with the exception

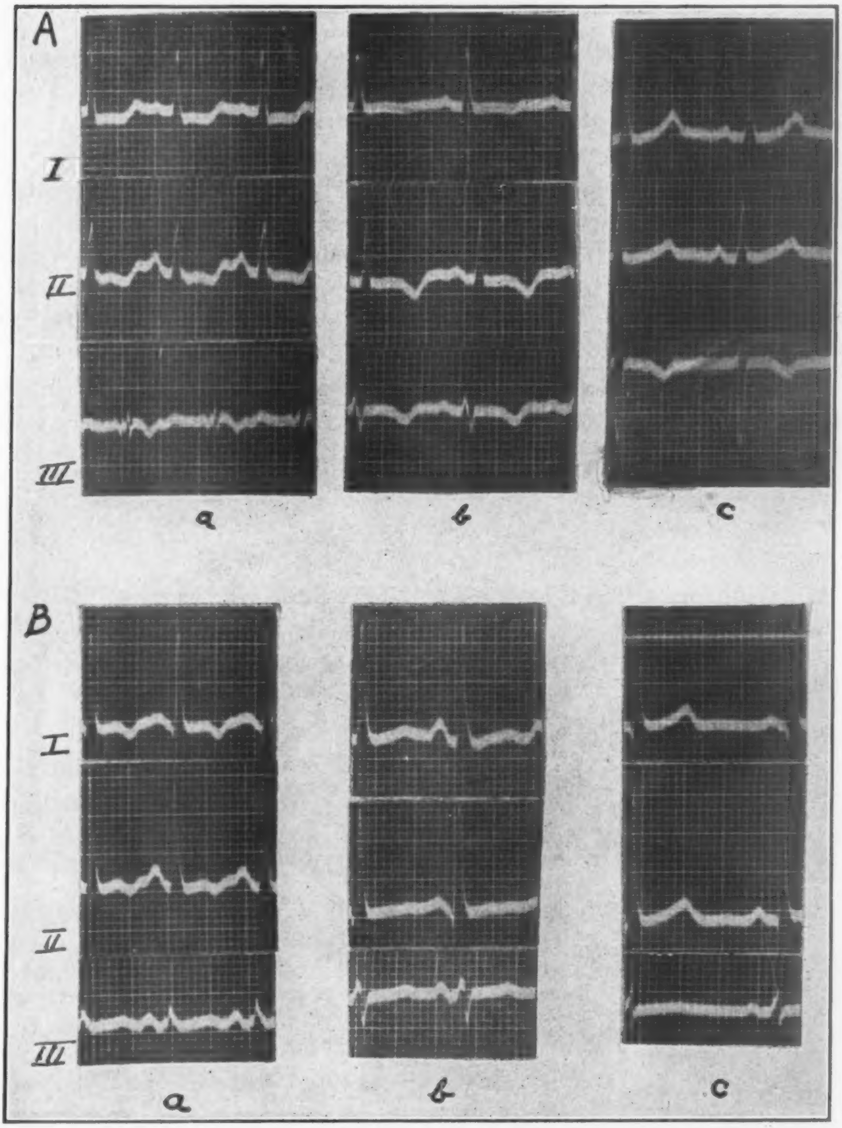

Fig. 4.—*A* (Case 6): *a*, Tracing made June 19, 1935, at 2:15 P.M., two hours after admission in coma. Note depressed and slightly inverted T_1 and inverted T_2. *b*, Tracing made June 20, 1935, at 4:25 P.M., twenty-two hours after patient was out of acidosis. Note slightly inverted T_1 and inverted T_2 and T_3 and absence of S-T depression. *c*, Tracing made June 24, 1935, at 11:30 A.M., practically normal with exception of left axis deviation.

B, case of acidosis, etiology undetermined (no insulin administered): *a*, Tracing made Jan 23, 1935, at 4:10 P.M., twenty hours after admission in acidosis. The CO_2 combining power of the blood on admission was 13 volumes per cent; at the time this tracing was taken it had returned to normal, being 63 volumes per cent. *b*, Tracing made Jan. 24, 1935, at 9:15 A.M., shows flattened T_1 and depressed S-T_2. *c*, Tracing made Jan. 28, 1935, at 5:30 P.M., is comparatively normal.

that the Q-T interval was not prolonged (Fig. 4*B*). We regard this one case as important since it shows that profound electrocardiographic changes can occur in and after emergence from ketogenic acidosis without insulin administration.

SUMMARY AND CONCLUSIONS

1. Except for a repeated study in one case, electrocardiographic changes were observed in every one of our 17 cases of coma and in 6 cases of precoma studied by serial electrocardiograms during and upon emergence from diabetic coma.

2. The electrocardiographic changes of the coma cases were graded as severe in 8 cases, moderate in 6 cases, and slight in 3 cases; the electrocardiographic changes in 6 precoma cases were similar although less severe than were the changes of those patients who entered the hospital in coma. Only one showed severe electrocardiographic changes; 4, moderate changes; and one, slight changes.

3. The chief alterations observed were lengthening of the Q-T interval, depression of the S-T interval, and inverted T-waves. Alterations in the QRS complexes were infrequent.

4. In all except 3 cases of the entire series of diabetic acidosis, the electrocardiogram eventually returned to normal.

5. The most abnormal electrocardiographic changes were observed not during coma but about twenty-four hours later when the patient was clinically improved and out of the acidotic state.

6. Serial electrocardiographic studies may be an important method of gauging the severity of cardiac disturbance during and upon emergence from diabetic coma.

7. The significance of these findings is discussed.

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CARDIAC SYNCOPE

Concerning the Clinical Differentiation of Its Types

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CONSIDERABLE interest has been aroused in recent years concerning cardiac syncope, its nature, and the prevention of attacks. It has become fairly well recognized that these seizures are due to the occurrence of episodes of transient ventricular standstill or fibrillation, and certain opinions concerning the recognition and treatment of these attacks have been put forward. On account of the obviously limited opportunity for the study of these transient seizures, it seems wise to discuss this subject in the light of observations made on a case herein reported.

In ventricular standstill, the more common of these conditions, it has been fairly well established that epinephrine and ephedrine are effective in preventing the seizures, a marked stimulus to rhythmic ventricular rhythm resulting, as shown by Nathanson. Less clear is the ideal therapy for the prevention of recurring attacks of ventricular fibrillation. Dock,[1] Morawitz and Hochrein,[2] and Nathanson[3] affirm that quinidine diminishes the tendency to ventricular fibrillation by decreasing the irritability of the ventricles. On the other hand, Schwartz and Jezer[4] report two patients with complete auriculoventricular dissociation who were subject to recurrent attacks of ventricular fibrillation and who during periods of freedom from attacks regularly responded to intravenous quinidine with the development of ventricular fibrillation or prefibrillatory arrhythmia.

While controversy may exist over the treatment of these conditions, their clinical differentiation, if possible, is nevertheless important in this consideration. Since both of these conditions are usually found in connection with complete auriculoventricular dissociation, the basic heart rates are generally slow. In ventricular standstill, while observation prior to an attack may occasionally reveal the presence of dropped beats or premature contractions, the usual course of events is the sudden cessation of ventricular activity without warning, as described by numerous observers.

In transient ventricular fibrillation, little was known regarding the mechanism and possibilities of recognition clinically until the studies of Schwartz and his coworkers[5] were brought out. These showed that there is usually a change in the course of events for an appreci-

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able time, usually several hours, before the onset of an attack. This starts with a gradual acceleration of both ventricular and auricular rates, the pulse rising to about 50 to 60 beats per minute. Then the intrusion of increasing numbers of ectopic beats of varying ventricular foci, left and right, occurs, producing a marked arrhythmia. This may be interrupted by a few isolated fibrillatory movements, and then the attack begins.

These observations would make it appear possible clinically to differentiate these conditions, since no irregularity simulating the pre-

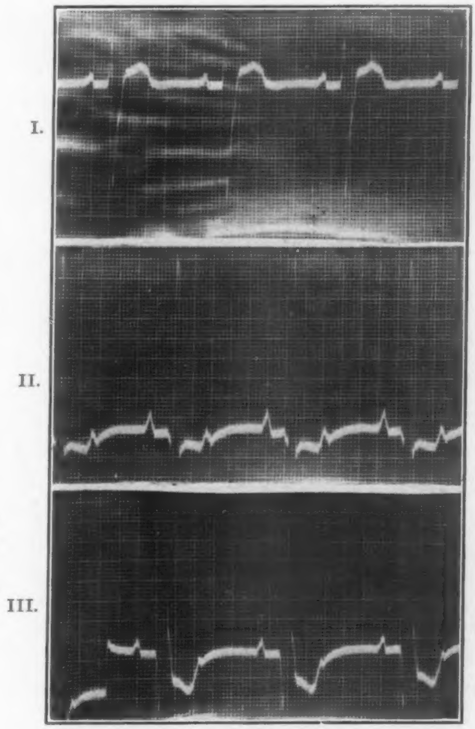

Fig. 1.—Record taken Feb. 27, 1933, showing right axis deviation. S-T is elevated in Lead I, depressed in Leads II and III, and 2:1 heart-block is seen.

fibrillatory type has been found described in the literature, although Schwartz, in a personal communication, recently states that he has seen several records of patients with auricular standstill, which showed introductory arrhythmias similar to those preceding ventricular fibrillation.

The study of a patient subject to recurring attacks of ventricular standstill which were preceded by an arrhythmia similar to that described as a prefibrillatory mechanism will therefore cast doubt upon this method of clinical differentiation, and seems worthy of report.

CASE REPORT

J. S., aged twenty-six years, was admitted to Bethesda Hospital, St. Paul, on July 9, 1935. He was a student and a trumpet player by occupation, and had always been well until January, 1933. At that time he developed acute coryza but worked daily. His sister was suffering from chickenpox, and he was said also to have had this disease although no rash appeared. Two days after this diagnosis was made, he fainted while reading a newspaper. He was observed by his brother to be very pale, rigid and breathing heavily. He was unconscious one-half hour. The next day he consulted his physician who had an electrocardiogram taken, a diagnosis of left bundle-branch block and two-to-one heart-block being made. The heart rate was 70 per minute. He did not complain otherwise, but following this the

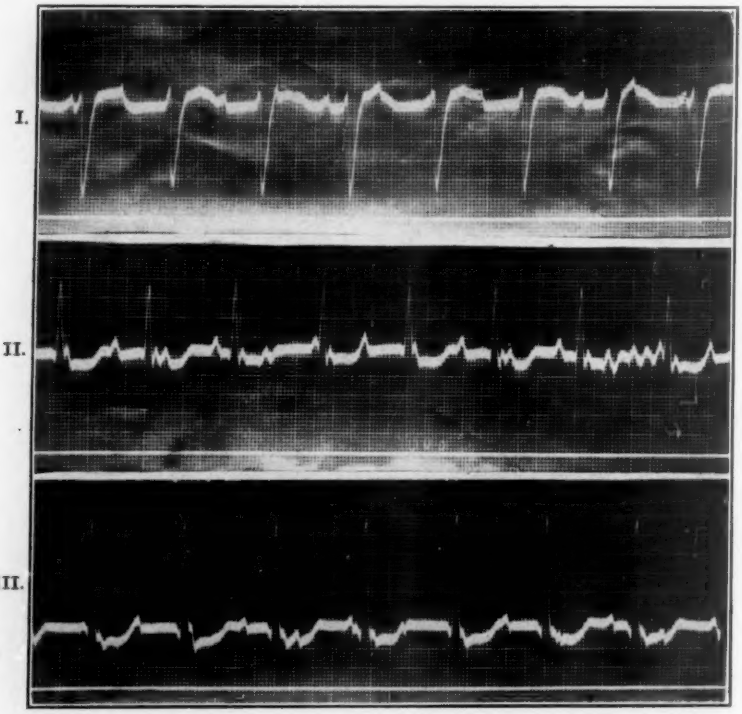

Fig. 2.—Record taken July 11, 1935, between attacks of syncope, patient being comfortable. This shows essentially similar wave contours, but a complete auriculo-ventricular dissociation with bundle-branch block has appeared.

attacks recurred about once a week. In February he consulted another physician who told him he had congenital heart disease. A week later he consulted a third physician who prescribed ephedrine sulphate, grains ⅜, three times a day. He then felt fairly well until June, 1933, when he began to have a recurrence of frequent attacks especially at night. These occurred as often as every 2 or 3 minutes lasting ½ to 2 minutes each. He was sent to Abbott Hospital, Minneapolis, where the attacks were prevented by the use of epinephrine. He was again returned home where the attacks occurred at irregular intervals, and fear of them caused him to remain in bed for two years. Intervals of as long as two months occurred between attacks. On July 4, 1935, he had a series of severe attacks which were not relieved by adrenalin as well as previously. On July 9 he had a very severe attack, a condition resembling status epilepticus, and was admitted to the hospital.

Physical examination revealed a well-nourished and well-developed young man, who showed no significant findings except for the heart. This was moderately enlarged to the left. The rate varied from 48 to 60 per minute and the rhythm appeared normal. There was heard a soft systolic murmur at the apex, not transmitted, and the second pulmonic sound was accentuated. The blood pressure was 140 mm. systolic, 100 mm. diastolic.

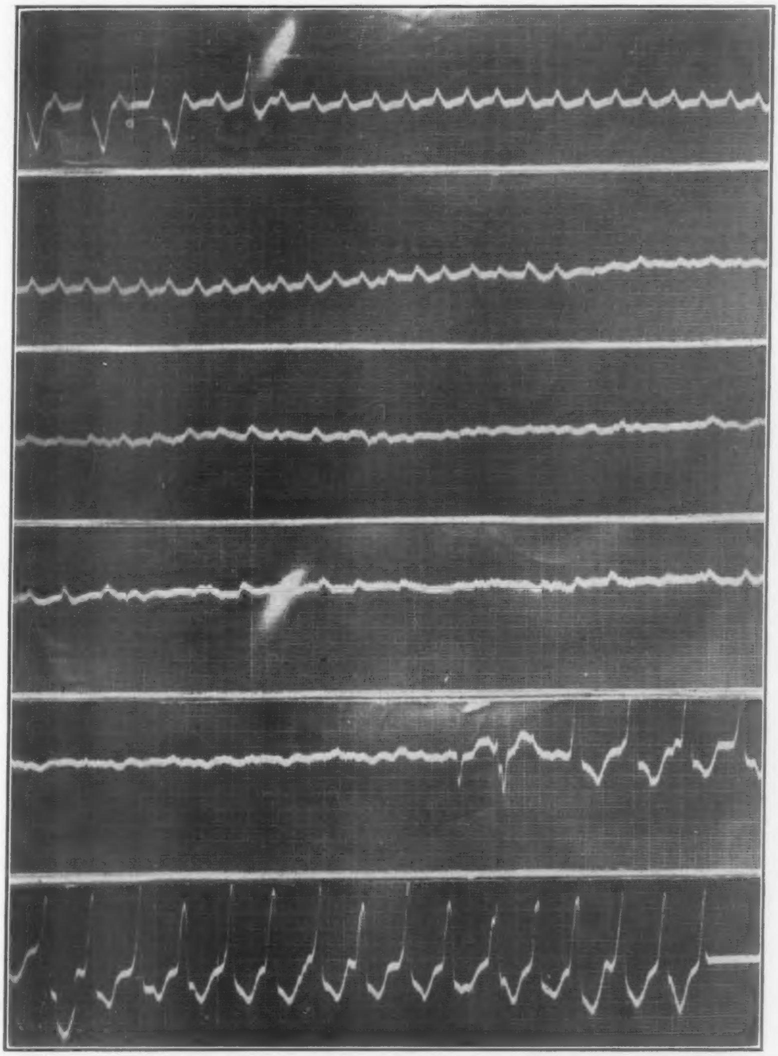

Fig. 3.—Continuous strip record of Lead II showing the onset, duration, and cessation of an attack of ventricular standstill and syncope lasting 43 seconds. Preceding the onset there is a complete heart-block with several beats from a ventricular focus, followed by a period of auricular contractions which gradually disappear. Effective ventricular contractions are initiated by two bizarre complexes of right ventricular origin, followed by a left ventricular tachycardia with a probable shifting of the focus of stimulus.

Repeated attacks of syncope occurred for twenty-four hours after admission, each lasting as long as several minutes. These were so severe that intracardiac injections of adrenalin, cardiac needling, or severe precordial blows were necessary to start

A.

B

C.

D.

E.

F.

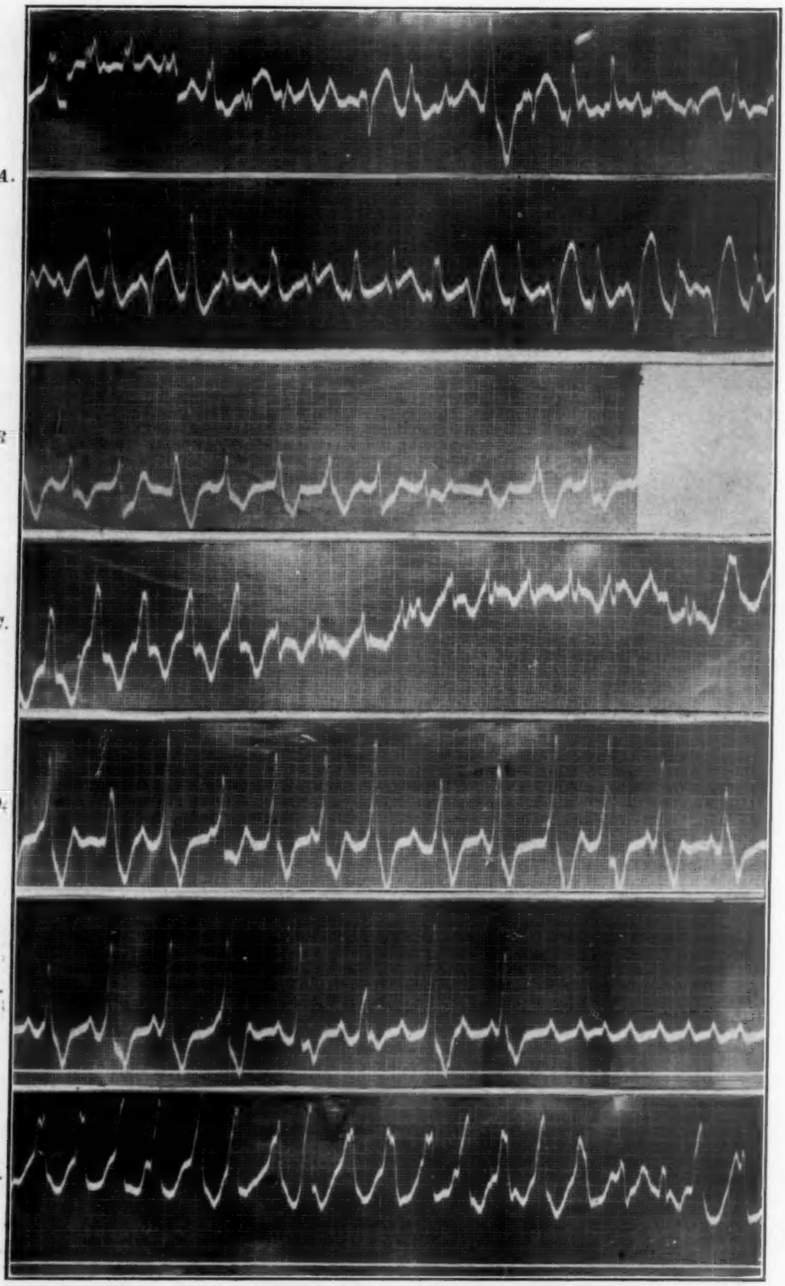

Fig. 4.—Records of Lead II showing the bizarre type of rhythm preceding various attacks. *A*, Continuous strip record; *B, C, D, E, F*, other examples showing the irregular ventricular rhythms which preceded different attacks.

cardiac activity. They occurred at intervals of a few minutes to one-half hour. Thereafter the attacks ceased, apparently being controlled by frequent 5 minim doses of adrenalin subcutaneously. He improved considerably although he was disoriented for about three days. On July 13 the attacks recurred with great frequency for about twenty-four hours, then diminished, and he felt fairly well until July 16 when they reappeared as often as every one-half minute, persisting for eight hours when he died in an attack, intracardiac adrenalin being of no avail. Autopsy was refused.

Immediately prior to the attacks of syncope there could be made out a variety of different heart rhythms. These were usually irregular, observation at times suggesting extrasystolic arrhythmias, at other times auricular fibrillation. The rate was usually accelerated from 80 to 120. These rhythms suggested very much the types described by Schwartz and his coworkers as prefibrillatory rhythms, and had it not been for the previous benefit obtained by the use of epinephrine, one would have been hesitant to use it. Electrocardiograms taken before, during, and after attacks show the bizarre and variable arrhythmias which occurred. These are shown and described in Figs. 1 to 5. Except for Figs. 1 and 2, as shown, all records are from Lead II.

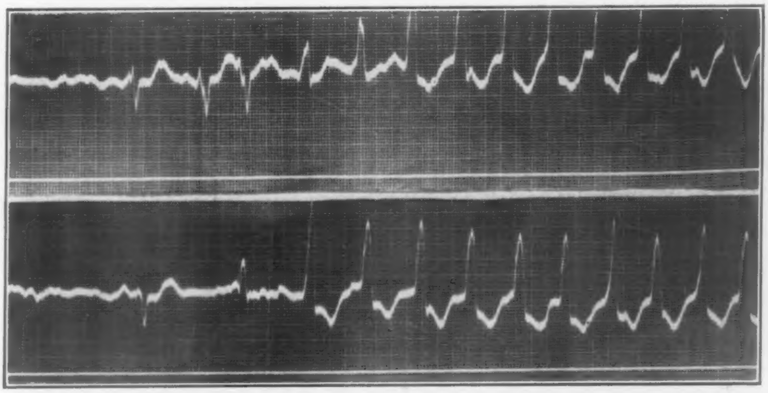

Fig. 5.—Two records showing the mechanism of cessation of the attacks. After a few bizarre contractions a fairly regular ventricular tachycardia begins. This would gradually become slower and a type of rhythm illustrated by Fig. 2 would appear.

DISCUSSION

It is hoped that the report of this case may add to the accumulating information regarding the mechanism of cardiac syncopal seizures and their proper interpretation and treatment. A paucity of reports has made difficult their proper evaluation.

Epinephrine is becoming widely used in the treatment of Adams-Stokes seizures, regardless of the fact that there is usually no knowledge of the mechanism of the attacks. Schwartz and Jezer have demonstrated the tendency of this drug to produce prefibrillatory states and attacks of transient ventricular fibrillation in patients who have been known to be subject to the latter spontaneously. Nathanson's experimental work supports these observations. It is therefore important to watch carefully the effect of this drug on patients with such seizures in whom the mechanism has not been definitely established.

In conclusion it may be pointed out that it is apparently unsafe to judge from a study of rhythm immediately preceding an attack the mechanism which may be responsible for its production. As far as is known, no clinical observation can accurately determine this and electrocardiographic study during an attack may be necessary for absolute certainty.

SUMMARY

Attention is called to a prevailing opinion that a study of the mechanism of the attacks of transient cardiac syncope will differentiate them as caused by ventricular standstill or ventricular fibrillation.

A case of recurrent ventricular standstill in a young man with complete heart-block, in whom the mechanism of the attacks resembled that of transient ventricular fibrillation, is reported.

It is suggested that such differentiation is probably not possible clinically without electrocardiographic records.

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ARTERIOVENOUS ANEURYSM*

Report of a Case With Pronounced Electrocardiographic Changes

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ELECTROCARDIOGRAPHY has attracted little interest concerning its relationship to the cardiac disability of arteriovenous aneurysm. An extensive review of the literature shows that several investigators have included clinical and experimental electrocardiograms in their studies (Lewis and Drury,[1] Gage and Hermann,[2, 3] Reid,[4] and others). The abnormalities, however, were so slight that little was to be said about them. Compression of the aneurysm with slowing of the pulse (Branham's bradycardiac phenomenon) has invariably appeared in the electrocardiogram as a simple prolongation of the diastolic pause. As noted by LaPlace[5] in a recent report, it is surprising how few electrocardiographic changes take place even when the heart is severely affected. Nevertheless, marked changes do take place though they are seen only in the last stages of the cardiac decompensation. Tracings showing these marked abnormalities have rarely been published or described—though an enormous amount has been written about arteriovenous aneurysms.

These defects, which may be acquired or congenital, are probably much more common than is generally supposed. Rienhoff[6] in 1923 found more than 500 reported cases (24 congenital) and since that time there are many more on record. Matas[7] has records of 41 (10 cerebral type) and Pemberton[8] states that 25 patients were operated on at the Mayo Clinic between 1915 and 1926 (16 acquired and 9 congenital). More than 75 cases of communication between the aorta and vena cava have been reported (Shennan,[9] Hartman and Levy[10]). Three arteriovenous aneurysms were of mycotic origin,[11] and several have been produced purposely[12] in the hope that the pressure in aorta would be reduced and aortic aneurysms relieved of strain.

Until twelve or fifteen years ago, the truly detrimental effects of these fistulas were unknown and prior to that time cases were reported primarily in regard to their surgical care. The heart disability, if observed, was thought to be coincidental.[13] From the reports of hundreds of these cases, it is obvious that many had no heart disability. Most of those seen by Makin[14] were of such recent origin that the cardiac disturbance had not developed. Then, too, all the cerebral and

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most of the congenital cases have had no cardiac complications, which is probably true of any small one in the periphery. Some writers have stated that none of the congenital fistulas show cardiac changes, but Lewis[15] cites several instances[16] including one case seen by himself, disproving this idea. According to Thomason,[17] Callander's[18] analysis of 447 cases disclosed only 16 having cardiac hypertrophy. Matas,[7] however, found cardiac signs or symptoms in 70 per cent of his 31 cases, after the 10 cerebral cases had been excluded. Thus we see that cases with cardiac changes are far from common and of those with cardiac hypertrophy, in only a few were electrocardiograms made. Few of these tracings have been published.

CASE REPORT

White male, aged forty-five years, a stone and cement worker, was admitted to hospital Oct. 26, 1935, complaining of severe shortness of breath and swelling of the entire body. He had been fairly well until about one year previously when, following an accidental fall on his back, he began to have shortness of breath, though he was not hurt by the fall. He continued to do some work until one month prior to admission. After reconsideration he remembered that he had slight dyspnea and palpitation as far back as 1917 and had been rejected from the army on account of his heart. In 1912, he had been accidentally shot in the right groin and left hip and though he had soon noticed a vibration or buzzing feeling in the right leg, this extremity did not swell or cause any particular trouble until some years later (1927), when a large sore formed on the inner lower side and would frequently return following the slightest injury (near the internal malleolus). The swelling of this leg began and became more and more pronounced. During the past year, he had three attacks of pain in the epigastrium and lower sternal region, not radiating. They were associated with exertion. After these spells he noticed some tenderness in the region of the liver. Slight jaundice was noted about one month prior to admission.

Past History.—He always did hard work and was seldom sick except during the past few years when he had been frequently hospitalized on account of slight injuries to the affected leg which did not heal readily. He had bronchopneumonia in 1932 with uneventful recovery and influenza in 1922. He denied rheumatic fever, scarlet fever, diphtheria, or syphilis. He was married and had five living children. His father and mother were living and well, aged sixty-eight and sixty-five years respectively.

Physical Examination.—Pulse was 120; respiration, 20; temperature, 98.6° F; he was a well-developed white male with obvious dyspnea, cyanosis, anasarca, and slight jaundice. The edema involved the face, and the abdomen was so tense that it could not be palpated satisfactorily. The lower legs were enormously edematous and practically of equal size. No dilated veins were visible or palpable in the right leg or abdomen, but there was a large discolored area just above the internal malleolus on the right, apparently the site of an old varicose ulcer. Just below Poupart's ligament on the right, an intense thrill could be palpated over an area about 5 in. by 6 in. This area showed no enlargement and the pistol bullet scar was so small it was scarcely visible. Auscultation over this area revealed a very loud continuous machinery or humming murmur with systolic accentuation. This sound seemed best transmitted upward and also toward the lower, outer portion

of the leg. With firm pressure over this area, these signs ceased; the pulse rate decreased from 120 to 60 (Branham's[19] bradycardiac phenomenon). The blood pressure increased from 130/80 to 160/80. At no time was a murmur discernible over the heart. There was typical evidence of auricular fibrillation, and this was

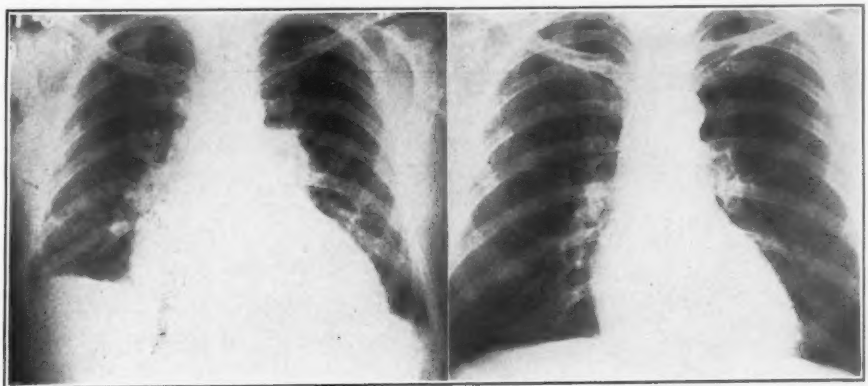

Fig. 1. Fig. 2.

Fig. 1.—Before operative cure of the aneurysm. Midsternum to the right heart border, 6.8; midsternum to the left heart border, 13.3; chest, 31.

Fig. 2.—Seventy-six days after operation. Midsternum to the right heart border, 4.7; midsternum to the left heart border, 10.3; chest, 31.7.

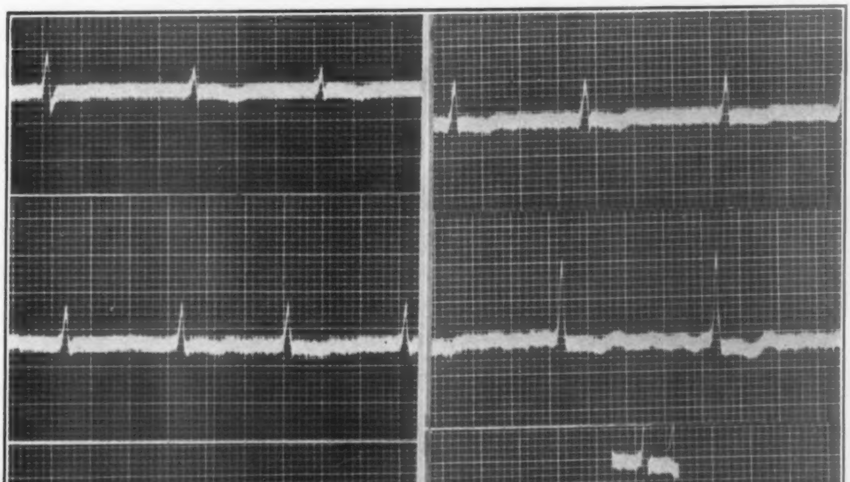

Fig. 3. Fig. 4.

Fig. 3.—Before operation, diminished voltage, T-waves almost isoelectric in all leads. Ventricular rate, 100. Auricular fibrillation. Digitalization incomplete.

Fig. 4.—Nine days after operation, increased voltage, decreased rate.

not affected by compression of the fistula except as to rate. Blood pressure of the affected leg could not be ascertained. Blood pressure of the other leg was 200/70; right arm, 150/80; left arm 160/80. Cardiac dullness was markedly increased ex-

tending, in the sixth interspace, about 14 cm. to the left of the midsternal line. The apex impulse was not visible and was quite feeble. The heart sounds were soft, indistinct, particularly at the base, and there was complete arrhythmia. Peripheral arteries were not thickened appreciably. The liver was believed to be quite large but could not be palpated satisfactorily. No pronounced pulsation of the liver was detected.

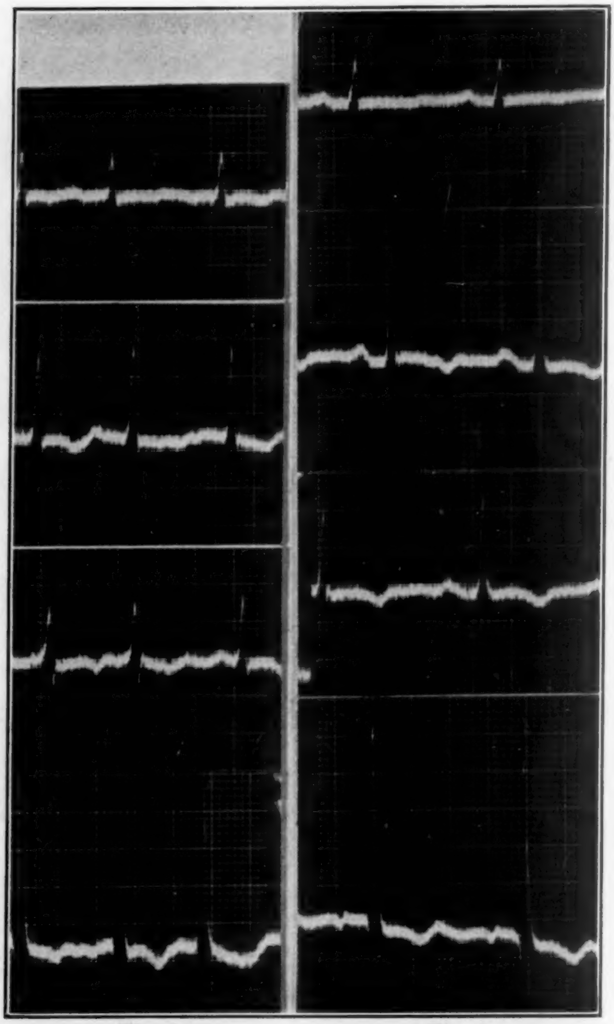

Fig. 5. Fig. 6.

Fig. 5.—Forty-six days after operation. Ventricular rate increased during quinidine therapy.

Fig. 6.—Forty-seven days after operation. Normal rhythm restored. Quinidine discontinued. T_2 and T_3 more deeply inverted, T_4 diphasic.

Laboratory Findings.—Wassermann reaction was negative; urine specific gravity, 1.017; very faint trace albumin, a few white blood cells and a few granular casts. Other urinalyses were negative. Leucocyte count was 12,600; polymorphonuclear leucocytes, 71; lymphocytes, 23; monocytes, 4; eosinophiles, 1; basophiles, 1; hemoglobin, 90 per cent (Tallqvist); nonprotein nitrogen, 66.6; creatinin, 1.8.

X-ray Findings.—(6 ft.) Heart greatly enlarged. Measurements: chest 31 cm.; midsternum to right heart border, 6.8 cm.; midsternum to left heart border, 13.3 cm. A great deal of hypostatic congestion evident (Fig. 1).

X-ray films taken after operation showed marked decrease in the size of the heart. Though an x-ray film made nineteen days after operation showed a very pronounced reduction in the heart shadow, a subsequent film, seventy-six days after operation, showed still further decrease (Fig. 2).

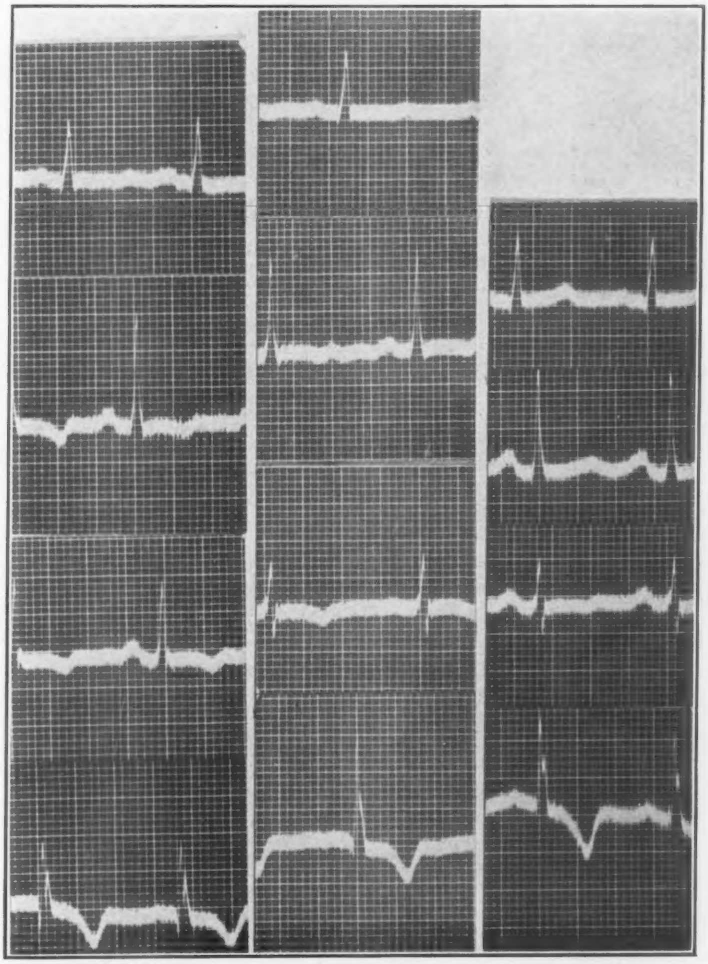

Fig. 7. Fig. 8. Fig. 9.

Fig. 7.—Eighty-eight days after operation. Eighty-four days after digitalis was discontinued and 41 days after quinidine was discontinued.

Fig. 8.—Ninety-five days after cure of aneurysm. T_1 upright. Depth of T_2 diminished.

Fig. 9.—One hundred twenty-three days after cure of aneurysm. T_2 has become upright, T_3 almost isoelectric, Q_4 has not improved.

Electrocardiograms showed pronounced abnormalities which had not completely returned to normal 123 days after operation (118 days after digitalis had been discontinued).

The series of changes which took place is interesting. The first electrocardiogram, Fig. 3 (prior to operation), showed diminished voltage, and there was an occasional ventricular ectopic beat. The T-waves were slightly inverted in all leads, almost isoelectric. At the time of this first tracing, 25 c.c. of tincture of digitalis had been given by mouth. However, since the average S-T segment did not show a typical digitalis effect, and with a rate of 100, it was believed that a full digitalis effect had not been obtained.

Following the operation, the voltage promptly increased, T_2 and T_3 became more deeply inverted, and T_1 gradually became upright (Figs. 4 to 9). More than three months after the operation T_2 became upright and T_3 showed evidence of beginning this change. Lead IV, when first observed, showed a very small Q and a somewhat flattened T which soon became diphasic and then normal. QRS_4 at the time of the last tracing showed no evidence of returning to normal. It had developed some notching, and Q_4 was even smaller than on previous occasions.

Course and Treatment.—Morphine was administered immediately and digitalization begun. When some slight improvement was noted, salyrgan was given intravenously on three occasions with definite benefit, and, though the patient continued very ill and uncomfortable, he appeared to be practically edema free, and both ankles were almost of normal and equal size.

He seemed to be in optimum condition on Nov. 22, 1935, and surgical correction of the fistula was carried[20] out. He reacted well, and during the night following the operation there was noticeable diuresis (1400 c.c.). Each day there was rapid clinical improvement. The fibrillation continued and was allowed to do so until Jan. 7, 1936, forty-six days after the operation. It had been allowed to continue in order to determine whether or not it would cease spontaneously. Digitalis had been discontinued four days after operation since there was such excellent improvement and the pulse was so slow. On Jan. 7, 1936, quinidine, gr. iii, was given at bedtime and the next morning gr. vi every two hours. Normal rhythm, restored after the fourth dose, continued until discharge from the hospital. All subjective symptoms of congestive failure had disappeared in little more than two weeks following the operation, and the patient rapidly gained strength and weight, though he did have rather frequent respiratory infection. The nonprotein nitrogen was only 33.3 and the creatinin, 1.8, Nov. 2, 1935, and 40.5 and 1.6, respectively, on Dec. 19, 1935. On Feb. 7, 1936, the blood pressure was 140/80; March 9, 169/98; and at time of discharge, March 25, 1936, the blood pressure was 150/90 and pulse, 80. His heart decreased to normal size; the electrocardiograms returned almost to normal; the signs of decompensation were absent.

At time of discharge there were occasional musical râles over both lungs and evidence of mild asthmatic bronchitis. The affected leg developed very slight edema after standing, but this edema subsided during the night. Aside from these mild disabilities he was a normal healthy person.

COMMENT

Though electrocardiograms showing pronounced abnormalities are rare, a comparison of the few available shows some more or less uniform and striking Q and T changes which suggest that the myocardial derangement is similar to that found in coronary disease or occlusion (not, however, meeting all specifications of Wilson and his coworkers[21] for recent occlusion). In the case reported by Fotheringham and Alvarez,[22] there was a deep Q_3 and inverted T_3 of the coveplane type which disappeared twenty-one days after the operation. In Reid's[4] experimental work Dog No. 9 lived thirty months after the

fistula was opened and was finally found dead. An electrocardiogram made eighteen months after opening the fistula showed no abnormality, but twelve months later, and less than a month before the dog died, an electrocardiogram showed a deep Q_1 and a deeper Q_2, T_1 inversion of the cove-plane type, and definitely depressed R-T segments in Leads II and III. This tracing today would suggest coronary occlusion of the Q_1 T_1 type. Details of the autopsy were not given except for the fact that there was hypertrophy.

In the case presented here the most noteworthy features are the diminished voltage, T-wave inversion, small Q_4 with slight widening and notching of QRS, auricular fibrillation (see illustrations).

Two outstanding ideas have arisen since 1920, explaining the mechanism responsible for the onset of cardiac dilatation and hypertrophy in these cases. Extensive clinical and experimental observations have been made by the chief exponents of each. Holman[23] contends that the cardiac dilatation and hypertrophy are the result of increased work, consequent upon increased venous pressure and increased volume flow through the heart. Lewis and Drury[1] do not agree that there is increased venous pressure except that resulting from congestive failure. They maintain that the cardiac disorder is the result of diminished coronary flow with deficient myocardial nutrition. It is suggested that the ideas of Lewis and Drury are given support by electrocardiograms of long-standing, far-advanced cases. Matas[7] has had one patient die of angina pectoris and coronary occlusion shortly after the operation on the fistula. He points out that this should be a likely situation for the development of coronary occlusion if the ideas of Lewis and Drury are correct.

A brief discussion of certain clinical features of the present case follows: A similar absence of the blood pressure in the affected limb was noted in the case of Dean and Dean[24] and a decreased pressure has been noted by others.[1, 25] An enormous urinary output immediately after the operation was observed by Reid.[26] The diastolic pressure in the present case was unusually high throughout, though cases have occurred in which there was associated hypertensive disease of severe degree.[27] The absence of any marked blood pressure (diastolic) response during Branham's phenomenon can be explained only by the observation of Matas[7] that decompensation may be so severe that there is no response, though it is possible that, with an originally high diastolic pressure, no marked response may be expected. Tachycardia, which is often present and which has been explained as resulting from engorgement of the splanchnics,[28] is in many cases absent. Auricular fibrillation is said by some[29] to occur frequently, and Matas says that arrhythmia is often present. However, descriptions of auricular fibrillation in these cases are difficult to find. In Thomason's[17] case, auricular fibrillation developed suddenly twenty-

three days after the fistula had been cured, and Matas had three patients who developed paroxysmal tachycardia (a similar condition[30]) shortly after their operations, showing the soundness of Holman's[31] advice that a prolonged convalescence is indicated.

SUMMARY

Cardiac decompensation has been reported in a rather small percentage of all cases of arteriovenous aneurysm. Even when there is severe decompensation, the electrocardiogram often shows few changes. Published electrocardiograms showing marked abnormalities are very rare.

A case is presented showing pronounced abnormalities in the electrocardiogram. Tracings were made prior to surgical cure of the aneurysm and after the operation, over a period of 123 days. They showed a remarkably slow return to normal, though clinical improvement was rapid. Auricular fibrillation in this case did not cease spontaneously after operation but ceased with quinidine therapy, and showed no inclination to return.

Other cases on record having decidedly abnormal electrocardiograms are compared with the present case. Certain clinical features of this case are compared with other cases from the literature.

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Department of Clinical Reports

A PROVED CASE OF DEXTROPOSITION OF THE HEART, SHOWING LEFT AXIS DEVIATION IN THE ELECTROCARDIOGRAM*

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IN DEXTROPOSITION of the heart, as in mirror-picture dextrocardia, the expectation is that the electrocardiogram would show a right axis deviation when the apex points to the right. In the case here presented, on the contrary, a left axis deviation was found. A survey of the literature revealed several other reports with a similar axis deviation:

1. A case reported by Owen cited by Lichtman[1] of complete situs inversus with mitral stenosis and left ventricular preponderance.

2. A case reported by Gorter[2] of congenital dextrocardia complicated by congenital malformations showing left axis deviation (in this case due to deep Q_2 and Q_3).

3. A case reported by Meyer[3] of congenital dextrocardia complicated by congenital malformations, showing marked right ventricular hypertrophy and left axis deviation (proved by autopsy).

4. A case reported by Abrahamson[4] of mirror-picture dextrocardia with left ventricular preponderance.

The unusual combination of dextroposition and left axis deviation in our case shows the difficulties of explaining the electrocardiographic findings on the usual concept of the Einthoven equilateral triangle.

CASE REPORT

The patient was first seen in the Mandel Clinic in February, 1931. He complained of dyspnea on exertion, weakness and productive cough. During childhood he had frequent attacks of "croup." At the age of seventeen years he contracted pneumonia and pleurisy. His complaints date back to that illness.

The physical examination at that time revealed an undernourished, narrow-chested white male, twenty-seven years old. Cardiac dullness was noted on the right side, and a forceful apex beat was visible just underneath the right nipple. A short, rough systolic murmur was heard over the base. There was impaired resonance with diminution of breath sounds and moist râles over both lung bases. A pleural friction rub was heard on the left side.

The x-ray examination showed the heart, lungs, trachea, and mediastinum pulled over to the right side. There was marked haziness of the lungs, and bronchiectases

*From the Heart Station, Michael Reese Hospital, Chicago.

were seen with several cavities and extensive adhesions. There was no situs inversus of the abdominal or thoracic organs. The findings were confirmed by fluoroscopy on a subsequent examination.

During the course of the next few years, he had several severe flare-ups of bronchitis but otherwise enjoyed relatively good health and was able to work until March 3, 1936, when he suddenly developed dyspnea and weakness which confined him to bed. On the morning of March 8 he was suddenly seized by extreme weakness and dyspnea and became cyanotic. He was brought to the hospital in the

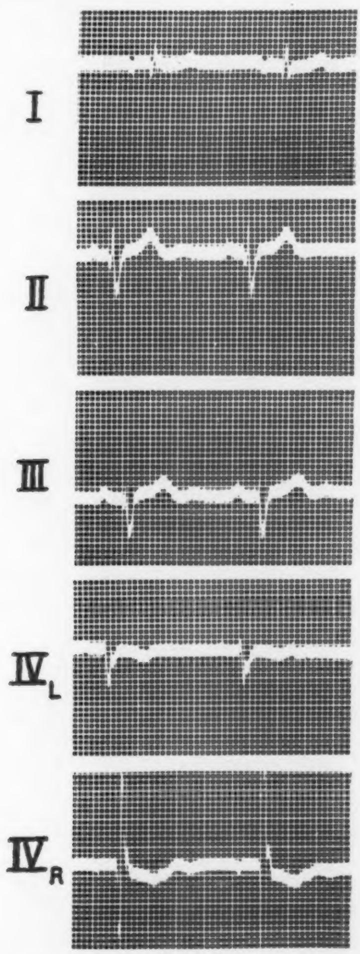

Fig. 1.—This is an electrocardiogram obtained in this patient. The standard leads are labeled I, II and III. IV_L is a standard Lead IV employed by us with the distant electrode on the left leg and the precordial electrode in the fourth interspace to the left of the sternum. IV_R is a lead similar to the previous one with the precordial electrode in the same interspace but to the right of the sternum.

afternoon and admitted on Dr. J. Meyer's service. Digalen, morphine, atropine and caffeine were given, and he was put in an oxygen tent. In spite of every effort, he became stuporous and died two hours after admission.

Autopsy Report (by Dr. O. Saphir).—The heart was displaced to the right and rotated on its long axis, so that the entire heart lay to the right of the sternum. The left lung was markedly emphysematous. Adhesions were present between the

pleura and the pericardium. The heart weighed 280 gm. The mitral valve showed evidence of an old healed mitral valvulitis. The coronary arteries were normal. There was a marked right ventricular hypertrophy. The lungs showed bilateral early bronchopneumonia and marked chronic bronchiectasis in addition to emphysema.

Electrocardiogram.—The curves taken May, 1935 (Fig. 1), and the one taken six months later were almost identical. The outstanding abnormalities were the negative P-wave in Lead I, the marked left axis deviation with QRS inverted in Leads II and III and small in Lead I, the marked slurring and notching of QRS in the standard and precordial leads, and the S-T elevation in Leads II and III. The inversion of QRS in Lead IV_L (the standard Lead IV with precordial electrode in the fourth interspace to the left of the sternum) and the occasional diphasic T in this lead, as well as the notched T in Lead IV_R (where the precordial electrode is in the fourth interspace to the right of the sternum) were all abnormal.

DISCUSSION

While most cases of mirror-picture dextrocardia, congenital dextrocardia without reversal of the heart chambers and dextroposition show right axis deviation, a few, of which this is an example, show the reverse. In this case, as in the one reported by Meyer[3] and presumably also in that of Gorter,[2] there is in addition a marked right ventricular preponderance. Several explanations suggest themselves.

It may be assumed that the combination of right ventricular hypertrophy and shift of the anatomical axis to the right has led to a rotation of the electrical axis of more than 180°. This seems rather improbable.

It is more likely that a counter-clockwise rotation of the heart around its longitudinal axis might be responsible. Such rotation has been shown to cause left axis deviation in animal experiments (Ackerman and Katz[5] and Meek and Wilson[6]) and in man (Nathanson[7] and Katz and Robinow[8]).

Recently, in this laboratory (Katz[9]) we have come to believe that such unexpected findings may be accounted for by changes in the relation between the heart and the structures surrounding it. These structures, namely, the diaphragm, the lungs, the great vessels, the anterior chest wall, and the muscles in front of the spinal column, are not equally good electrical conductors (Katz and Korey[10]). The contact of the different regions of the heart with the good conductors is largely responsible for the appearance of the electrocardiogram (Katz, Gutman, and Ocko,[11] Katz, Sigman, Gutman, and Ocko[12] and Robinow, Katz, and Bohning[13]). In our case there is not only a shift of the heart as a whole to the right but also a shift of some of the structures surrounding it (viz., the lungs and large vessels) and a modification of the contact between the heart and the good electrical conductors (the posterior muscle mass, the diaphragm, and the anterior chest wall). These factors may have altered the electrical field of the body sufficiently to give rise to the left axis deviation.

This case, therefore, is another link in the chain of evidence obtained in this laboratory, supporting the idea of the importance of the nature and the location of the electrical conductors adjacent to the heart and disproving the general applicability of the Einthoven triangle concept.

This case illustrates again that left axis deviation, even of marked degree, is not necessarily associated with a shift of the anatomical axis to the left or with left ventricular preponderance. It may be found with the exact opposite as in the cases here reviewed or in cases with brown atrophy (Katz, Saphir, and Strauss[14]).

SUMMARY

A case of dextroposition of the heart with right ventricular hypertrophy proved post mortem is presented because there was in the electrocardiogram marked left axis deviation. The significance of this finding is discussed.

I wish to thank Dr. L. N. Katz for his guidance in preparing this case report.

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CARDIAC RUPTURE ASSOCIATED WITH METASTASES TO THE HEART FROM CARCINOMA OF THE DUODENUM*†

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THE chief interest in the case reported in this paper lies in the fact that rupture of the heart was occasioned by metastatic carcinoma. Of minor interest are the facts that the primary tumor occurred in the duodenum, a site in which the occurrence of carcinoma is comparatively rare, and that there existed, coincidentally, the end stages of rheumatic heart disease, the patient being in a state of extreme decompensation when death occurred.

Because the patient had been under observation and treatment for rheumatic heart disease for a number of years, the gastrointestinal symptoms were readily attributed to the state of cardiac decompensation, and the tumor of the duodenum was not recognized clinically. The death was clearly cardiac, and, when the case came to postmortem examination, there was nothing to indicate that anything beyond the typical pathological changes of rheumatic heart disease would be revealed.

CASE REPORT

W. B. M., a white man, aged forty-eight years, entered the hospital on Oct. 25, 1930, complaining of dyspnea, palpitation and headache.

Family History.—Mother died of cancer of the stomach; father died of kidney disease; three sisters and one brother living and well; one sister had heart trouble. Marital history was negative.

Past History.—The patient had the usual diseases of childhood. There was no history of scarlet fever or rheumatic fever; however he had had rheumatic pains in various joints for many years; he had gonorrhea in 1898 and influenza in 1918.

Present Illness.—The patient stated that he had known he had heart trouble since 1923, when a physician told him he could never do manual labor again. Since that time he had become exhausted on slight exertion and experienced palpitation in the epigastrium on exertion or after eating a heavy meal.

For the past three years he had been incapacitated for work.

Physical Examination.—Physical examination showed a well-developed, poorly nourished man. He was pale and the lips were cyanotic. The chest showed marked muscular atrophy and bilateral restricted motility. The resonance was impaired in both upper lobes posteriorly and breath sounds were subdued.

The examination of the heart showed the apex in the sixth interspace, 3 cm. to the left of the midclavicular line. The heart was greatly enlarged to the left and downward. A loud diastolic rumble was transmitted to the axilla, ending in a loud first sound immediately followed by a soft second sound.

At the base was a soft, systolic murmur heard first in the right interspace. The rhythm was irregular, and the volume of the sounds varied greatly. The blood pressure before exercise was 110/58; after moderate exercise it was 110/60, and the lips showed increased cyanosis.

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†Read before the Los Angeles County Pathological Society, January 14, 1936.

Abdominal examination revealed nothing of interest, nor did examination of the genitals, rectum, or extremities.

The clinical diagnosis of mitral insufficiency and stenosis, with possible tricuspid disease and chronic myocarditis was established. Repeated Wassermann tests were negative. The report on the roentgenographic examination was cardiac hypertrophy and old pleuritis. The electrocardiographic examination on Oct. 30, 1930, revealed auricular fibrillation with evidence of myocardial damage. The patient was given digitalis, and a second electrocardiogram on Nov. 13, 1930, showed evidence of digitalization.

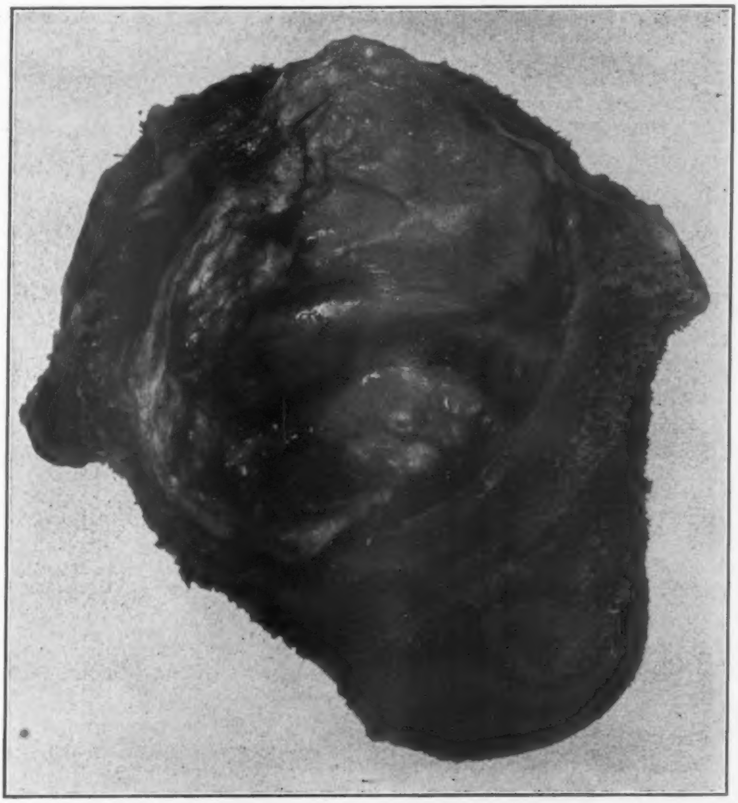

Fig. 1.—Heart, lateral wall of auricle dissected away. Note tumor infiltration of wall, the calcified "fish mouth" type of mitral valve, and the shaggy hemorrhagic exudate covering the epicardium.

The patient was in the hospital for the next three and one-half years. At times he was better and at times worse. He suffered a dull, precordial pain, which at times became sharp, and he required hypodermics on several occasions.

Against advice, he insisted on leaving the hospital in April, 1934. He was readmitted a few weeks later stating that while he was away the pain became worse, he suffered marked vertigo and blurring of vision and could not take care of himself. He developed a chronic cough with sputum, and a marked degree of bloating and heartburn. A burning, epigastric pain developed one to two hours after meals, and he vomited blood on several occasions. Sippy powders gave him no relief. The patient gradually displayed signs of congestive heart failure with edema of the extremities.

The treatment was supportive and symptomatic. Digitalis and sedatives were given as indicated. Decompensation was marked by May, 1934. Cardiac distress became increasingly severe. The patient had been in a relative state of comfort until Oct. 31, 1935, when he suffered "an attack of pain in the heart, difficult breathing and a feeling of internal spasm" (the words of the nurse on the chart). From this time until his death he complained of great agony and received a constant succession of hypodermics of morphine.

He rapidly became moribund and died Nov. 17, 1935. The cause of death was ascribed to cardiac failure in rheumatic heart disease.

Post-Mortem Examination.—The body was that of a well-developed, slightly emaciated, white male.

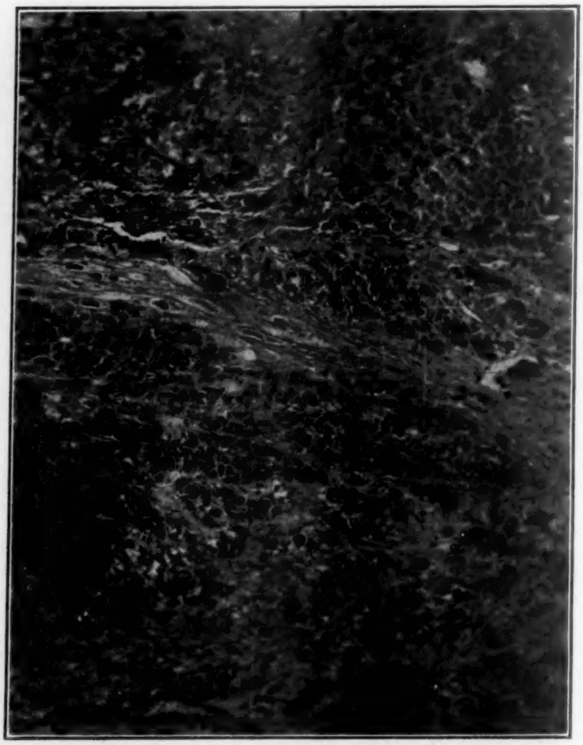

Fig. 2.—Section of duodenum showing the diffuse infiltrating character of the tumor. (×150.)

Heart.—The pericardial sac was enormously distended, extending from the left anterior axillary line to the right beyond the right sternal border, and was filled with dark red blood clot, and some free unclotted blood, measuring in all about 500 c.c. The heart was greatly enlarged. The surface was covered with reddish, fibrinlike material which was quite firmly adherent to the epicardium. It had the gross appearance of hemopericardium. The heart weighed 700 gm. The left auricle was enormous, measuring 10 cm. in diameter. It was firmly adherent to the parietal pericardium, and, when an attempt was made to remove the heart, the auricular wall tore and a large portion remained attached to the parietal pericardium. The wall of the auricle was thickened to 8 mm. The endocardial surface was covered with a verruca-like growth which covered practically the entire endocardial surface, including the surface of the mitral valve. It also apparently involved the entire wall of the auricle and showed evidence of ulceration. The point of rupture was found on the posterior wall in the portion that was adherent to the pericardium.

There was marked hypertrophy of the left ventricle and a moderate degree of hypertrophy of the right ventricle. The mitral valve showed a fish-mouth type of deformity. The leaflets were fused, leaving a narrow slit, 4.5 cm. in length. The fused leaflets were thickened and showed evidence of calcification. The surface of the valve was covered with the same verruca-like material found involving the wall of the auricle and covering the endocardial surface. The aortic valve showed evidence of some old inflammatory lesion, probably rheumatic. The leaflets were partially fused with a beadlike effect on the edges of contact, causing stenosis and insufficiency. The pulmonary and tricuspid valves showed no gross lesion aside from dilatation. There was quite marked coronary atherosclerosis and moderate atherosclerosis of the aorta.

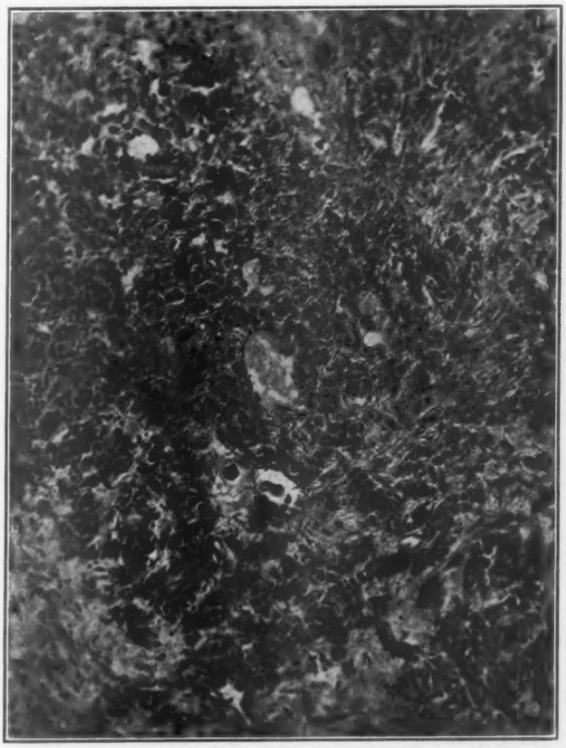

Fig. 3.—Section taken from the heart wall showing a morphological structure identical to that seen in the duodenal tumor. (×150.)

Lungs.—The combined weight of the lungs was 1,280 gm. Both showed the same picture, a number of ragged adhesions and on section a number of small patches of bronchopneumonia at each base. Mediastinal nodes were not enlarged.

Abdomen.—The peritoneum was smooth; there was no free fluid and no evidence of glandular enlargement. The liver weighed 1,700 gm. It was rather mottled, soft, and friable and on section the nutmeg markings of chronic passive congestion were noted. The spleen weighed 140 gm., was red and quite firm; on section it showed quite marked passive congestion. There was a red infarct at the upper pole, measuring 1 cm. in diameter. The gallbladder, adrenals, pancreas, bladder, prostate, and testes showed no gross pathological lesion.

Genitourinary Tract.—The combined weight of the kidneys was 250 gm., both showing the same picture. The capsule stripped readily, leaving a surface with a number of deep infarction pits. These pits were old and healed. On section

the cortex was rather thin and somewhat irregular. There was a mild vascular thickening.

Gastrointestinal Tract.—The stomach was slightly dilated, otherwise it showed nothing unusual. On the posterior wall on the duodenal side of the pyloric ring, there was noted a small ulcer 5 mm. in diameter. The walls and base were indurated, and the edges were crateriform. The lesion showed active ulceration with some bleeding. The remainder of the gastrointestinal tract showed no gross pathological change. The regional lymph nodes were not enlarged.

Microscopic Examination.—Sections of the duodenal wall at the region of the tumor showed a diffuse, infiltrative type of newgrowth. The cells were round, oval, or polyhedral and showed marked variation in size. The nuclei were relatively large and somewhat hyperchromatic. For the most part the cells were growing in columns and cords and infiltrated diffusely. There was some attempt at alveolar formation, but for the most part it was quite anaplastic. There was practically no desmoplasia. It was noted that the mucosa at the site of the lesion is gastric, rather than duodenal in type. The transition of the characteristics of the gastric to the duodenal mucosa is gradual and, in this instance, while the lesion was geographically duodenal, it was histologically gastric.

Heart.—The myocardium of the left auricle was infiltrated by epithelial cells having the same appearance as those noted in the tumor of the duodenum. Certain microscopic fields in the auricular muscle and in the duodenal tumor were identical in appearance. The endocardium of the left auricle was covered with a layer of closely packed epithelial cells of the same appearance. A section through the mitral valve revealed old fibrosis, calcification and some degeneration. The endocardium of the auricular surface of the valve showed a superimposed layer of anaplastic epithelial cells, identical to those seen in the auricular muscle and in the duodenal tumor. The microscopic study of sections of the various other organs did not reveal evidences of tumor.

COMMENTS

Metastatic carcinoma in the heart is not rare, but it is most frequently a part of a generalized dissemination, rather than the only demonstrable site as in this case. Burke[1] reports a series of fourteen cases found at autopsy among 327 cases of known malignancy. In none of these cases was the metastasis confined to the heart. Our experience is in accord with that of Burke, Heninger,[2] and others, who note that it is practically impossible to diagnose the condition during life. Burke states that the cases in his series had been studied for a period of time prior to death, that x-ray plates of the chest had been made at intervals, and that there was nothing to suggest the presence of metastasis. Osler[3] notes that secondary tumors of the heart are usually without symptoms, even when the disease is extensive.

Rupture of the heart is a rare occurrence in consideration of the great frequency of pathological conditions of the heart. It is, however, not so rare as a scarcity of the report of cases in the literature would indicate. Krumbhaar and Crowell[4] (1925) collected 654 cases. Davenport[5] (1928) was able to collect 710, 35 of which had been reported since 1925 and 50 of which had been omitted by Krumbhaar and Crowell. Spontaneous rupture of the heart is, in the overwhelming majority of cases, the result of coronary disease, and is precipitated by thrombosis or embolism. Benson, Hunter, and Manlove,[6] in

a recent paper stress that, while the outstanding cause of cardiac rupture is coronary sclerosis, rupture of the heart may occur if the myocardium is weakened by disease other than that of the nutrient arteries. These authors note that rupture caused by gummas of the heart have been described chiefly in the older literature. Also, there are authentic reports of rupture caused by lesions of tuberculosis.[7] Among the rare causes of cardiac rupture may be listed echinococcus disease.[8]

The case of cardiac rupture caused by metastatic carcinoma reported in this paper is without parallel in the literature, as far as we can ascertain.

Benson, Hunter, and Manlove note malignancy as a possible cause of cardiac rupture but add that Mayer was unable to find such an instance in the reports to 1888, and Jores in 1924 failed to find any in the more recent literature. In the series studied by Krumbhaar and Crowell, a melanotic sarcoma is ascribed as the cause of cardiac rupture. The reference is not given, and there are no details of the case. In 72 per cent of the series of Krumbhaar and Crowell, death was described as sudden. They note that in certain rare cases, death was reported as occurring days or weeks after the rupture and in one case a month later. Osler described a case of rupture in which the man walked up a steep hill after the onset of symptoms and lived for thirteen hours. In the case reported in this paper, it would appear that the rupture occurred on Oct. 31, 1935, at which time the patient was stricken with severe agony which never ceased until death occurred seventeen days later.

SUMMARY

Metastases to the heart from a primary carcinoma in the duodenum weakened the myocardium and precipitated cardiac rupture in a patient with rheumatic heart disease. The case is without parallel in the literature, as far as we can ascertain.

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ORTHOSTATIC HYPOTENSION TREATED WITH BENZEDRINE*

Report of Case

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ONLY about twenty-two satisfactory cases of orthostatic hypotension are on record. The first inklings of this curious syndrome are to be found in C. Laubry's brief mention[1] of a case which was referred to him in 1891 by Babinski. The patient, a man forty-eight years of age, suffered from vertigo and astasia abasia, but no evidence of disease of the central nervous system could be found. Quite by accident, Babinski discovered that the patient's arterial pressure was unusually low, whereupon he sent him to Laubry, whose careful observations demonstrated beyond question the orthostatic nature of the hypotension. In 1932, after Bradbury and Eggleston's definitive study[2] had established the essential characteristics of the syndrome, Laubry[3] reported his case in greater detail.

The pathogenesis of orthostatic hypotension, as Grace Roth[4] points out in her excellent discussion, is still largely a matter of speculation, and no uniformly successful treatment has been discovered. Although ephedrine has helped somewhat in a few cases, including our own, it has failed more often than it has succeeded. Our use of a new drug, together with the fact that the number of recorded cases is so small, prompted us to report the following additional case.

REPORT OF CASE

History.—The symptoms developed in characteristic fashion. In 1930, at the age of fifty-eight years, the patient, whose health had always been excellent, noticed for the first time that he was losing his strength and endurance. His appetite began to fail, and his weight declined slowly, but he did not become completely disabled until, in 1933, he began to experience attacks of faintness, sometimes attended with actual vertigo. He soon discovered that these attacks never occurred except when he was on his feet and could be terminated promptly by sitting or lying down. They kept recurring with increasing frequency, and eventually became so severe that syncope supervened. He always regained consciousness almost as soon as he fell, and, except for transitory weakness, or unless injured by the fall, as he was on several occasions, felt none the worse for the experience. Fatigue was obviously not a factor in these attacks, for they were more likely to occur upon first arising in the morning than at any other time of the day, but there was no doubt about the influence of hot weather, which intensified all the symptoms to such an extent that it was almost impossible for the patient to get on his feet. Yet he never had

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heat stroke or heat exhaustion. It was perhaps more than a coincidence that, when he became intolerant of heat, he lost the ability to perspire freely. Except for negligible areas in the axillae and lumbar region, his anhidrosis eventually became complete. Nocturnal diuresis, loss of libido, and impotence were additional features of the history.

The syncope was manifestly not epileptic, for it was not attended with convulsions, biting of the tongue, or foaming at the mouth, never occurred while the patient was asleep, and was not preceded by a true aura or followed by somnolence, mental confusion, and headache. Moreover, there was nothing in the history to indicate primary labyrinthine or other intracranial disease, and the fact that no pronounced abnormality of the heartbeat preceded or accompanied the syncope excluded the possibility of cardiac origin. The progressive asthenia, syncope, anorexia, and gradual loss of weight (20 pounds in the course of several years), together with a rather vague story of occasional nausea, vomiting, and colic, suggested Addison's disease, but there had been no abnormal deposition of pigment in the skin or unnatural craving for salt.

Physical Examination.—The patient was a white male, sixty-three years of age. About twenty-four hours before his admission to the University Hospital he was seized with an afebrile diarrhea so severe that when he arrived he was considerably dehydrated, barely conscious, and almost in shock. He had already developed several large hemorrhoids and shortly after admission passed a liquid stool mixed with dark red blood. (Subsequent investigation led to the conclusion that the hemorrhoids must have been responsible for this gross bleeding, as well as for the traces of blood which were present in the feces for months thereafter. This continual loss of blood was probably a factor in his secondary anemia.) With the passage of this bloody stool the diarrhea came to an abrupt end; the patient had never experienced anything of the kind previously, and he has not suffered a recurrence. On admission the arterial pressure measured only 60/40 mm. Hg, but under the circumstances such a low level attracted little attention, more especially because, with the patient confined to bed, it rose to normal within a few days.

After the patient recovered from his acute enterocolitis he was wide-awake and cooperative. The skin was extraordinarily youthful and almost milk white. The sclerae were not icteric. The pupils reacted satisfactorily to light and in accommodation, and the fundi were negative to ophthalmoscopic examination. The head was covered with a plentiful growth of gray hair. The ears, nose, face, lips, tongue, buccal mucosa, palate, and pharynx were not remarkable. The teeth were carious. There was no enlargement of the thyroid gland or cervical lymph nodes. A lipoma of moderate size was present on the nape of the neck.

Examination of the lungs revealed no modification of their extensibility, volume, or density, and no râles. The heart was not enlarged, and there were no endocardial murmurs, but the heart sounds were rather faint. The rate and mechanism of the heartbeat were normal. The aorta was not abnormally accessible. The volume and contour of the arterial pulse were normal. A moderate amount of peripheral arteriosclerosis was present. Examination of the abdomen showed no enlargement of the liver or spleen, no free fluid, and no adventitious masses. Rectal examination disclosed several large internal hemorrhoids. The genitals and extremities were entirely negative, and there were no signs of disease of the central or peripheral nervous system.

Laboratory Examination.—At the time of his admission, when the patient was considerably dehydrated, a somewhat paradoxical situation existed. Anhydremia might well have accounted for the presence in the urine of traces of albumin and a few casts, for the low carbon dioxide combining power of the blood (31.5 volumes per cent), and for the apparent retention of nitrogen (urea 71.4 mg. per cent, uric

acid 7.2 mg. per cent, creatinine 4.5 mg. per cent), but it was difficult to understand how dehydration as severe as this could leave the blood chlorides undisturbed (625 mg. per cent) and not cause an apparent increase in the hemoglobin and cellular content of the blood. The hemoglobin content was 72 per cent; the erythrocyte count, 3,790,000; and the leucocyte count, 9,400; and these figures did not change appreciably after the dehydration had been relieved. Furthermore, the apparent retention of nitrogen vanished completely within seventy-two hours (urea 17.5 mg. per cent, uric acid 4 per cent, creatinine 1.2 mg. per cent), but more than a week elapsed before the albumin and casts disappeared. It is therefore doubtful whether the initial acidosis and nitrogen retention were as pronounced as they were made to appear. Eleven subsequent estimations, made at intervals over a period of three months, never showed any retention of nitrogen.

The blood Wassermann reaction was negative. The gastric juice contained no free hydrochloric acid, even after the ingestion of alcohol and the subcutaneous injection of 1/44 grain of histamine. Roentgenologic examination disclosed no evidence of disease of the stomach, duodenum, colon, adrenal glands, lungs, heart, or aorta. The oxygen consumption was 10 per cent below normal. The electrocardiograms revealed nothing of importance; those made in the erect posture showed inversion of the T-wave in Lead III.

Subsequent Course.—The definite tendency toward hypotension, which became clearer as time went on, made it imperative to exclude, once for all, the possibility of Addison's disease. The fact that a large intake of salt and the administration of 5 c.c. of eschatin per diem for twenty-two days brought about no amelioration was perhaps not conclusive, but crucial evidence was obtained when a salt-free diet rich in potassium was tolerated by the patient for eleven days without the slightest aggravation of his symptoms. The plasma chlorides remained at a normal level throughout the period of chloride deprivation.

After it dawned on us that posture might have something to do with the patient's symptoms, it was discovered that a startling fall of arterial pressure occurred when he assumed the upright position. The following are illustrative of a long series of measurements made over a period of many weeks:

Supine	Sitting	Standing
112/85 mm.	85/60 mm.	55/40 mm.

The lowest pressures occurred in the mornings. Syncope threatened whenever the maximum systolic level fell to 55 mm. Hg, or below. Although the heart rate was not totally unresponsive to changes in posture and blood pressure, as it has been in so many of the cases previously reported, the extent of the response depended largely on what the rate was in the supine position. If it was 80 with the patient lying on his back, it might increase to 88 when he sat up, and to 100 when he stood on his feet, but, if it was 100 when he was recumbent, it did not accelerate appreciably as he stood up. Neither pressure on the carotid sinus nor the intravenous injection of $\frac{1}{150}$ grain of atropin had any effect on the heart rate or blood pressure. The administration of $\frac{1}{8}$ grain of pilocarpine by mouth exerted almost no diaphoretic effect.

In the midst of his hospital stay the patient developed severe pharyngitis and tonsillitis, accompanied by fever and prostration, and followed by widespread erythema multiforme, from which he recovered completely in two weeks' time.

Summary.—The principal features of the history were the progressive asthenia, anorexia, loss of weight, syncope conditioned on the erect posture, anhidrosis, intolerance of heat, nocturnal diuresis, loss of libido, and impotence, without evidence of craving for salt, pigmentation of the skin, epilepsy, intracranial disease, or disorder of the heartbeat. Examination by clinical and laboratory methods revealed

a pale, not abnormally pigmented skin, carious teeth, a lipoma on the nape of the neck, no evidence of heart disease, a not entirely normal response of the heart rate to changes in posture and blood pressure, orthostatic hypotension with syncope, slight peripheral arteriosclerosis, internal hemorrhoids, no abnormalities of the nervous system, slight secondary anemia, a negative blood Wassermann reaction, no nitrogen retention, achlorhydria, no roentgenologic evidence of disease of the alimentary tract or adrenal glands, a basal metabolic rate of -10 per cent, normal electrocardiograms, and no aggravation of symptoms with a salt-free diet rich in potassium.

Diagnoses.—Orthostatic hypotension; internal hemorrhoids; secondary anemia; intercurrent enterocolitis; intercurrent pharyngitis, tonsillitis, and erythema multiforme.

TREATMENT

The following table summarizes the effect of ephedrine and benzedrine on the arterial pressure. The measurements are representative of a large series; all of them were made at the same time of day.

TABLE I

	SUPINE	SITTING	STANDING
Untreated	112/85	85/60	55/40
Ephedrine			
48 mg. at 6 and 8 A.M.; 24 mg. at 10 A.M., 12 M., and 2 and 4 P.M.	140/88	130/80	80/60
48 mg. at 6, 8, and 10 A.M., 12 M., and 2, 4, and 6 P.M.	150/90	140/90	100/75
Benzedrine			
20 mg. at 5 and 6 A.M.; 10 mg. at 8 and 10 A.M., 12 M., and 2 and 4 P.M.	115/80	100/80	80/60
20 mg. at 6, 8, and 10 A.M., 12 M., and 2, 4, and 6 P.M.	115/80	100/70	70/55
40 mg. at 6 A.M.; 30 mg. at 8 A.M.; 20 mg. at 10 A.M., 12 M., and 2 P.M.; 10 mg. at 4 and 6 P.M.	140/95	120/80	75/65
Ad libitum	120/80	110/75	75/60

On the whole, the patient liked benzedrine better than ephedrine because it made him less tremulous, induced less insomnia, and was perhaps somewhat more effective in dispelling his weakness. However, if amounts of either drug sufficiently large to maintain the blood pressure within normal limits were employed for more than a few days at a time, it became difficult, even with full doses of the various barbiturates, to overcome the consequent insomnia. After the patient returned to his home he continued to take 100 to 150 mg. of benzedrine a day. Except in warm weather, this amount was sufficient to keep him comparatively comfortable. He felt better than he had for many years, and even began to perspire over his back and shoulders. No ill effects of continuous medication with benzedrine were noted.

COMMENT

Our experience in this case suggests that benzedrine is worthy of further trial in the symptomatic treatment of orthostatic hypotension. If it should not actually supersede ephedrine, at least it may prove to be a welcome alternative in some cases.

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Department of Reviews and Abstracts

Selected Abstracts

Bronk, D. W., Ferguson, L. K., Margaria, R., and Solandt, D. Y.: The Activity of the Cardiac Sympathetic Centers. Am. J. Physiol. **117:** 237, 1936.

The activity of the cardiac sympathetic centers has been investigated by recording the action potentials in the cardiac nerves from the stellate ganglia of the cat.

There is a fairly continuous discharge of impulses which exert a "tonic" augmentor and accelerator influence upon the heart. This discharge is, however, largely modified by changes in the chemical composition of the blood and by afferent impulses.

The principal pathways of the impulses from the cord to the stellate ganglion are the third and fourth and to a lesser extent the second and fifth thoracic rami.

The impulse frequency from the individual sympathetic motor nerve cells seldom exceeds ten or fifteen a second, and is usually considerably less. This contrasts with the much higher frequency of discharge from somatic motor nerve cells.

The potential pulses in the postganglionic nerves are of considerable magnitude because of the grouping of impulses which results from the innervation of many postganglionic fibers by a single preganglionic fiber.

There are also much larger potential waves caused by the synchronous activity in very many nerve fibers. It is shown that this is due to the coordinated and rhythmic discharge from large numbers of nerve cells in the centers. This activity is bilaterally synchronous.

The grouped activity is of four types. The volleys may come at irregular intervals or at other times periodically with frequencies varying from 5 to 20 sec. but unrelated to any other obvious rhythm of the organism. Or, on the other hand, the bursts of impulses may be synchronous with the pulse or the respiratory cycle.

The latter two forms of rhythmic cellular activity are largely due to afferent impulses from the viscera: bursts of impulses from the blood vessels initiated by the systolic rise in pressure or the impulses from distention receptors in the lungs.

An example of the marked effect of such afferent impulses upon the activity of the sympathetic centers is found in the observation that it is possible to drive those centers by repetitive stimulation of the central ends of the carotid sinus or aortic nerves, thus causing the motor nerve cells to discharge periodically with the frequency of the afferent impulses. This can be done within a limited range of stimulus frequencies.

The characteristically grouped discharges from the cardiac sympathetic centers cause periodic variations in heart rate only if the bursts of efferent impulses are separated by some seconds. This is due to the inertia of the effector mechanism.

AUTHOR.

Essex, Hiram E., Herrick, J. F., Baldes, Edward J., and Mann, Frank C.: Blood Flow in the Circumflex Branch of the Left Coronary Artery of the Intact Dog. Am. J. Physiol. **117:** 271, 1936.

By the use of the thermostromuhr of Rein, experiments have been made on the blood flow in the circumflex branch of the left coronary artery of the intact dog. Observations have been made over periods as long as fourteen days.

Epinephrine causes a transient but marked increase in coronary blood flow, amounting in some experiments to as much as four or five times the control values. The coronary blood flow is doubled by administration of nitroglycerin or amyl nitrite, but the effect is of short duration. In response to appropriate doses of thyroxin, increases in coronary flow as great as 244 per cent above the control values were observed forty-eight to ninety-six hours after injection.

During the digestion of a meat meal the coronary flow was increased to a degree comparable to what has been observed in other vessels of the body. Exercise on a treadmill produced an initial rapid augmentation in coronary flow, which declined to a lower level as the exercise continued but additional work induced by changing the angle of the treadmill again caused a temporary increase in coronary flow, which declined to a lower value as the same degree of exercise continued.

A significant correlation between heart weight and coronary flow or between pulse rate and coronary flow was not found.

AUTHOR.

Donal, John S., Jr., and Gamble, Clarence J.: The Cardiac Output in Man. Am. J. Physiol. **116:** 495, 1936.

The simultaneous values of oxygen tension and of carbon dioxide tension in the lungs were computed for hypothetical experiments of the type used in the triple extrapolation method of Redfield, Bock, and Meakins (1922) for estimating the cardiac output in man. When each computed value of carbon dioxide tension was plotted as a function of the computed oxygen tension, the points were found to lie on curves and not on straight lines as is assumed in the triple extrapolation method.

The plotting of analyses of successive samples taken during continuous rebreathing gave curves with the same characteristics as those calculated from theoretical considerations.

Pairs of such curves were constructed from experiments on ten subjects. When these were extrapolated by the linear procedure of the triple extrapolation method the venous tensions found were different from those indicated by the convergence of the curves. Because of the tensions in the rebreathed mixtures chosen for these experiments, these differences were greater for carbon dioxide than for oxygen.

Cardiac outputs of these subjects determined at the same time by the ethyl iodide method agreed more closely with a curved than with a linear extrapolation.

It is concluded from these results that when gases are rebreathed or held in the lungs, variations in carbon dioxide and in oxygen tensions cannot be assumed to be directly proportional to each other. In consequence, the triple extrapolation method for the estimation of blood flow which Redfield, Bock, and Meakins have based on such an assumption cannot be expected to give reliable results.

In eleven rebreathing experiments, return to the lungs of blood abnormally low in oxygen content was evident at an average time of 24.5 sec., after the beginning of rebreathing. Recirculation of blood high in carbon dioxide was less readily detectable and was not evident until a later time.

AUTHOR.

Pfuhl, Wilhelm: The Lapse of Cardiac Contraction as Affected by Intrathoracic Function. Deutsches Arch. f. klin. Med. **247:** 179, 1936.

The author states that the emptying of the heart by contraction of the muscle is a relatively simple phenomenon compared with the refilling of the heart during diastole. No original experiments are brought to bear on the subject. Older work is frequently cited, and the paper takes the form of a thorough discussion of the possible factors involved. The conclusions are, however, interesting. He believes that a considerable portion of the energy for filling the ventricles is derived from

the preceding systole in two ways: 1. The shortening of the ventricle pulls down the plane of the valves and draws blood into the auricles. 2. The decrease in size of the heart extends the lungs slightly, and these in returning to their previous state during the next diastole draw blood into the auricles. Then the auricle contracts and fills the ventricle. Only during auricular contraction, therefore, does blood cease to flow into the heart. He concludes also that high negative intrathoracic pressure, through increased filling of the heart, is associated with high systemic arterial pressures.

J. M. S.

Dieckhoff, Josef: The Capacity for Work of Hearts With Insufficient Aortic Valves With and Without Hypertrophy in Heart-Lung Preparations and the Effect of Digitalization. Arch. exper. Path. u. Pharmakol. **182**: 268, 1936. **The Sensitivity to Digitoxin and Strophanthin of Hearts With Insufficient Valves With and Without Hypertrophy.** Ibid. p. 285. **The Action of Thyroxin Upon the Capacity for Work and Upon the Strophanthin Sensitivity of the Cat's Heart.** Ibid. p. 292.

Consideration of these three papers together is done for brevity. Each investigation appears to have been planned and executed with care. The animals used were cats. The aortic valves were injured by the method of Rosenbach (thrusting through the valve from the right carotid artery a large club-headed sound). The hearts without hypertrophy were used within one to fifteen days. Hypertrophied hearts were used from 100 to 150 days after operation. The capacity of the hearts for work was tested in heart-lung preparations in three ways: first, by increasing the arterial pressure, second, by increasing the venous pressure (increasing the output), and third, by noting the duration of life of the preparation. Three to five preparations of each type of heart to be compared were used.

In the first paper (1) normal hearts and (2) hearts with aortic insufficiency without hypertrophy, and (3) with hypertrophy were examined.

The hearts with recently injured valves appeared to be impaired according to all three criteria, failing to maintain as high pressures or as large outputs or to live as long as the normal and hypertrophied hearts. The extraordinary capacity of the hypertrophied hearts was emphasized by an ingenious experiment. A rubber valve was substituted for the injured aortic valve. When this was done, the hearts with recently injured valves compared favorably with the normal hearts, and the hypertrophied hearts outlasted the normals in every way. The third series of experiments compared normal hearts with two groups of hearts whose aortic valves were recently injured. In one group the cats had been thoroughly digitalized in the four days prior to the making of the preparation. The capacity of the "prophylactically digitalized" hearts for work was decidedly better than that of the undigitalized hearts with aortic insufficiency but was less than that of the normal hearts.

The second paper deals with the lethal dose of digitoxin and strophanthin administered to the same types of hearts used in the preceding paper. In one set of experiments digitoxin was given to the whole animal, in another set, to heart-lung preparations. The results were clear. Before hypertrophy occurred in the hearts with aortic insufficiency, they exhibited approximately the same sensitivity to digitoxin or strophanthin as normal hearts. After hypertrophy occurred, the lethal dose was diminished by from 22 to 47 per cent and appeared to be related to the degree of hypertrophy. The difference between the group was so marked that whether the dose was reckoned on a basis of the weight of the whole heart, per gram of heart, or per kilogram of animal, made little difference to the conclusions. The results were the same in heart-lung preparations as in intact animals.

The third paper shows, by means of heart-lung preparations, employing the tests used in the first paper for comparing capacity for work, that this function diminishes when thyroxin is fed to the animals for ten days prior to the making of the preparation and that with longer feeding (three weeks) the decline is greater. Furthermore, the sensitivity to strophanthin of hearts of cats which have been receiving thyroxin for longer than three weeks is markedly increased. The conflicting reports of earlier workers on the question of whether thyroxin increases the sensitivity of the heart to the action of strophanthin are explainable because, when thyroxin has been fed for less than two weeks, no change from normal is found.

J. M. S.

Segura, Angel S.: Registration and Interpretation of Cardiovascular Activity in the Normal Infant. Rev. argent. d. cardiol. **3:** 3, 1936.

The most striking result obtained by recording optically the heart sounds in 120 normal infants from birth to two years of age was the finding of three sounds per cycle in a great proportion (38 per cent). The moment of occurrence of this third sound and its time relation with the ordinary first and second heart sound and with the P-wave of the electrocardiogram sufficiently warrant the assumption that it is due to auricular systole.

The phonocardiographic records show that the first heart sound of infants and young children has a duration ranging between 0.064 and 0.172 sec., with the majority of the results falling between 0.10 and 0.14 sec., the fundamental frequency being very constantly of about 40 per second. The first heart sound is the most intense on the mesocardiac area.

The second heart sound lasts for between 0.045 and 0.164 sec., the majority of the results ranging from 0.055 to 0.10 sec., its fundamental frequency being also about 40 per second.

The auricular sound (visible in 38 per cent of the cases and easily recognizable as vestigial vibration in another 31 per cent of the total number) is 0.06 ± 0.001 sec. before the onset of ventricular systole. It lasts for about 0.057 sec. and shows a fundamental frequency of about 40 per second (average$=39 \pm 0.68$). The intensity of the auricular sound is the lowest as compared with that of the other sounds.

No true reduplication of either the first or the second sound was ever recorded. There was no instance in the records of the so-called physiological third heart sound.

The duration of the silent periods between the first and second sounds and between the second and the following first was practically the same in all cases.

AUTHOR.

Segura, A. S.: Registration and Interpretation of Cardiovascular Activity in the Normal Infant. Rev. argent. de cardiol. **3:** 85, 1936.

Fontanellar Pulse.—Optical tracings (Frank's method) of the fontanellar pulse are easily obtained in infants after the first month of life. The record is somewhat similar to that of the central arterial pulse recorded in adults. It affords important information concerning the rhythmicity of the heartbeat and (if recorded with the heart sounds) the approximate duration of the isometric contraction and ejection phases. The fontanellar pulse starts between 0.04 to 0.05 sec. after the first heart sound, this interval increasing with the age. The same relation can be found with the top of the R-wave of the electrocardiogram simultaneously recorded. The ascending limb is relatively steep, forming a 95° to 110° angle with the horizontal.

Femoral and Tibial Pulses.—An optical record may be obtained by means of a pneumatic cuff, a sphygmoscope, and a segment capsule. The record in both cases

shows a quite simple contour with no evident dicrotic wave. The femoral sphygmogram, showing a rounded top during the first days of life, tends to become angular with the increase of age. It starts between 0.072 to 0.084 sec. (averages according to different ages) after the beginning of the first heart sound. This delay may be still longer in older children. The ascending limb is less steep than the corresponding limb of the fontanellar pulse, the angle ranging between 101° and 130°, with the majority of the results falling between 105° and 125°. The tibial pulse record always shows a rather angular top, its amplitude is smaller, and its delay is longer (0.105 sec.) as compared with the femoral pulse record. Its ascending limb is still less steep.

AUTHOR.

Echague, E. Soaje: Electrocardiographic Alterations Produced by Typhoid Fever in Children. Rev. argent. de cardiol. **3:** 122, 1936.

Electrocardiograms recorded in 88 children suffering from typhoid fever showed frequent alterations in 53 per cent ± 3.5 of the patients under observation. The electrical axis was deviated to the right in 11.84 per cent ± 2.51 of the cases during the acme state, the fact coinciding with hypertoxic manifestations. There were not alterations of excitability, a sinus arrhythmia being observed only during convalescence in the proportion of 33.78 per cent ± 4.11. The A-V conduction time was altered in 10.20 per cent ± 2.35 of the patients during the acme and in 19 per cent during the convalescence. The QRS complex was widened during the acme in 2.63 per cent ± 1.06, and a low voltage of R-wave was encountered during the same period in 11.84 per cent ± 2.51 of cases, these alterations ceasing completely during convalescence. The alternations of T_1 and T_2 reached 18.42 per cent ± 3.01 and also disappeared altogether during the convalescence. Inversion of T_3 in 47.36 per cent ± 3.78 of the cases during the acme period diminished to 40 per cent ± 4.26 during convalescence and finally decreased to 31.06 after recovery. The inversion of P-wave and alternations of the A-V conduction time observed during convalescence always coincided with sinus arrhythmia, giving grounds to the belief that their origin might be imputed to an increased tonus of the vagus. The widening of P-R and QRS in the acme was probably due to toxemia since the alterations are no longer noted after recovery.

AUTHOR.

Schlomka, G., and Reindell, H.: Studies on the Physiological Irregularities of the Heart Beat. Ztschr. f. Kreislaufforsch. **28:** 473, 1936.

In young people mild and moderate exertion causes tachycardia but does not abolish sinus arrhythmia. The heart action and respiration are in a sense coupled, since, on one hand, the heart beats faster when the return of blood is greatest, and, on the other hand, the blood flow is fastest when the oxygen alveolar content is greatest, viz, at the end of inspiration. Rhythmic passive abdominal pressure modified the phasic respiratory sinus arrhythmia. This is taken to indicate that the Bainbridge reflex is an important factor in causing sinus arrhythmia.

L. N. K.

Misske, B.: The Electrocardiogram of the Myxedema Heart. Ztschr. f. Kreislaufforsch. **28:** 601, 1936.

Eighteen cases are reported with a review of the literature. Of these, eight cases showed a decreased QRS amplitude and six showed abnormalities of the P-wave and T-wave. Six cases, however, showed no change.

L. N. K.

Parkinson, John: Enlargement of the Heart. Lancet 1: 1337, 1936.

This subject was presented as the Lumleian Lectures for 1936, delivered before the Royal College of Physicians in London. It is an extensive review of the well-known facts of heart size and concepts of those influences which change this size, either in the whole heart or in particular regions. This is a full review of the accepted methods of studying cardiac enlargement and considerable emphasis is placed on radiological methods. Little mention is made of palpation in determining cardiac size. The article contains considerable information from the author's own experiences, particularly his analysis of the work of others which has been done under his direction.

The determination of the size of the heart still remains an interesting subject and one which is not yet fully explained. This article is an interesting contribution to the subject.

H. McC.

Clark, Eugene, and Berger, Adolph R.: Hemorrhagic Extravasations Into the Leaflets of the Atrioventricular Valves: Their Relationship to Pulmonary Embolism. Arch. Path. 22: 524, 1936.

Ecchymoses in noninflamed atrioventricular valvular leaflets were observed in four persons. In three who showed pulmonary embolism, the ecchymoses were limited to leaflets of the tricuspid valve. In the fourth, hemorrhages occurred beneath the mural endocardium and in the leaflets of the mitral and tricuspid valves. In all four, some of the ecchymoses involved the vascularized annuli, whereas others were limited to the distal, apparently avascular, regions of the leaflets. It is suggested that the ecchymoses which were limited to the leaflets of the tricuspid valve were related to the coexisting pulmonary embolism.

AUTHOR.

Struthers, R., R., and Bacal, H. L.: Rheumatic Infection in Childhood: Observations on the Sedimentation Rate and the Schilling Count. Canad. M. A. J. 35: 258, 1936.

Observations on 100 cases of rheumatic infection in childhood indicate that the sedimentation rate is a more satisfactory test for the activity of rheumatic infection than is the Schilling differential count. It has also the advantage of simplicity: it is not laborious, and it does not require special technical training. The sedimentation rate is also of greater sensitivity as an index of inactivity of rheumatic infection.

H. McC.

Jobling, James W., and Meeker, Dorothy R.: Further Investigations on Experimental Atherosclerosis. Arch. Path. 22: 293, 1936.

An unsuccessful attempt was made to accelerate and increase the development of cholesterol lesions in the aorta of the rabbit by the following injurious procedures added to cholesterol feeding: (1) intravenous injections of streptococcus toxin, (2) ammonium chloride feeding, (3) production of artificial fever, (4) intravenous injections of peptone, (5) induction of anaphylactic shock, and (6) intravenous injections of uric acid.

Similarly, no effect on the blood vessels of cats could be demonstrated when they were fed cholesterol and, in addition, were treated with (1) peptone or (2) histamine intravenously or were fed (3) ammonium chloride.

AUTHOR.

Landé, Kurt E., and Sperry, Warren M.: Human Atherosclerosis in Relation to the Cholesterol Content of the Blood Serum. Arch. Path. **22**: 301, 1936.

The concentration of cholesterol in the blood serum was compared with the degree of atherosclerosis in the aorta, as measured by the lipid content, in 123 healthy persons who had died suddenly from violence. No relationship was evident, and it is concluded that the incidence and severity of atherosclerosis are not directly affected by the level of cholesterol in the blood serum per se.

AUTHOR.

Bargen, J. Arnold, and Barker, Nelson W.: Extensive Arterial and Venous Thrombosis Complicating Chronic Ulcerative Colitis. Arch. Int. Med. **58**: 17, 1936.

One of the very serious complications of chronic ulcerative colitis is extensive thrombosis of the blood vessels. Among 1,500 cases thrombophlebitis or arterial thrombosis which was extensive enough to become a grave clinical problem occurred in 18. The last 6 cases are described in detail. Three of the 6 patients died. All of the deaths were believed to be caused by toxemia and not by embolism.

H. M.

Scupham, George W., and de Takats, Geza: Peripheral Vascular Diseases: A Review of Some of the Recent Literature and a Critical Review of Surgical Treatment. Arch. Int. Med. **58**: 531, 1936.

This is a carefully prepared, extensive review, which presents an important contribution to this subject. It is recommended for careful reading and is not subject to abstracting.

H. McC.

de Takats, Geza: Acute Arterial Occlusions of Extremities. Am. J. Surg. **33**: 60, 1936.

The differential diagnosis between embolism and thrombosis of peripheral arteries is discussed. Emphasis is laid on the importance of recognizing traumatic segmental vessel spasm and venous or lymphatic block with secondary vessel spasm. Evidence for a reflex arc of collateral vessel spasm is its interruption by novocaine block of peripheral nerves, by spinal anesthesia, and by sympathetic ganglionectomy. The afferent arc is postulated to consist of the ordinary sensory nerves, with which the vessels are well supplied, and the entire arc completed by way of the posterior root ganglion, the posterior root, the connector neuron to the lateral horn, and the ganglion cells of the efferent sympathetic fibers which are relayed in the sympathetic ganglionated trunk and go by way of the somatic nerves to the blood vessels.

The spasm which follows acute arterial occlusion can be relieved in some cases by the use of intravenous papaverine and by means of alternating negative and positive pressure apparatus. Of 5 cases treated by means of the former method, marked and lasting benefit was obtained in 3; in 5 by the latter, of which 3 were late and hopeless, a definite immediate benefit was not derived. Embolectomy should be resorted to early in selected cases, but not until after a brief trial with heat and papaverine.

H. M.

Collens, William S., and Wilensky, Nathan D.: Two Quantitative Tests of Peripheral Vascular Obstruction. Am. J. Surg. **34:** 71, 1936.

The authors believe that previous tests offer no information regarding degrees of vascular obstruction and are of no use in following the progression of vascularity in an extremity under treatment. They have devised two tests: (1) the venous filling time and (2) claudication time.

Changes in these times indicate changes in rate of blood flow.

H. M.

Lazarus, Joseph A.: Mesenteric Vascular Occlusion. Report of a Case of Complete Occlusion of Superior Mesenteric Artery With Involvement of Entire Small Intestine. Am. J. Surg. **33:** 129, 1936.

The case was that of a diabetic woman. There was complete closure of the main stem of the superior mesenteric artery by a thrombus and involvement of the entire small intestine, cecum, and ascending colon. An autopsy report is included.

AUTHOR.

Jirka, Frank J., and Scuderi, Carlo S.: Glomus Tumor. Report of a Case. J. A. M. A. **107:** 201, 1936.

This case, one of seventy in the literature, is briefly but adequately presented, and includes photographs of the histological slides. In this instance the tumor was on the inner aspect of the arm, of the size of a split pea, and with a pinhead-sized bluish area which was exquisitely painful when touched.

H. M.

Clark, Eugene, Graef, Irving, and Chasis, Herbert: Thrombosis of the Aorta and Coronary Arteries, With Special Reference to the "Fibrinoid" Lesions. Arch. Path. **22:** 183, 1936.

Homogeneous masses which exhibited the tinctorial properties of fibrin were frequently encountered on the surface and within the superficial fibrous regions of intimal aortic plaques of atherosclerosis and syphilitic aortitis.

In the lipoid zones of aortic plaques material which stained like fibrin frequently occurred in a fibrillar or homogeneous form. This material was commoner in ulcerated or eroded plaques, but it was present also in sections of plaques which appeared intact.

Homogeneous masses staining like fibrin were observed forming a layer between the formed elements of the thrombi and the plaques in eight of nine cases of parietal aortic thrombosis. In many instances identical masses were encountered within the fibrous or lipoid zones of the underlying plaques.

The evidence reviewed leads us to the belief that the homogeneous fibrin-staining ("fibrinoid") masses, occurring on the surface of fibrous plaques or the fibrous covering on atheromas, represent compressed and hyalinized blood elements and that the subsurface "fibrinoid" masses in most instances are the remnants of an organizing surface deposit. The "fibrinoid layer" beneath aortic thrombi represents laminated surface deposits of blood elements which have undergone a variable degree of organization.

It is suggested also that in other instances in which there is ulceration of the plaque or a loss of endothelial lining and a loosening and separation of the superficial collagenous fibers, the subsurface fibrin-staining masses may represent coagulated blood plasma which has penetrated the plaque from the lumen of the vessel.

As a result of repeated deposition of blood elements on the surface of the plaques and progressive organization of such hyalinized elements, the plaques of syphilitic aortitis and atherosclerosis may undergo a progressive increase in size. A thrombus of formed elements and orthodox configuration may frequently supervene on such laminated, hyalinized and partially organized surface deposits.

No differences could be discerned between the tinctorial behavior of these "fibrinoid" masses and that of the fibrinous component of thrombi. It is believed that these masses owe their tinctorial properties to their fibrinous component. There is no evidence at present to support the view that the deposits of homogeneous fibrin-staining material in the intimal aortic plaques of atherosclerosis or syphilitic aortitis represent altered or necrotic collagenous fibers.

Study of serial sections of eleven thrombosed coronary arteries has revealed differences in the character of the intimal plaque at the site of initial thrombosis. In some a fresh break in the inner collagenous lining of the atheroma was demonstrated; in others the fibrous lining was thinned out, and the collagen fibers were widely separated. In the presence of congestive heart failure the thrombi were deposited on intimal plaques which were apparently intact. In one case a fresh thrombus was deposited on a plaque containing partially organized surface deposits of blood elements.

We could find no evidence to support the view that the fibrin-staining material in the plaques of coronary arteries represents altered or necrotic fibrous tissue. As in the plaques of atherosclerotic and syphilitic aortas, such fibrin-staining masses either represent the remnants of an organizing surface deposit of fibrin or are due to the penetration into the plaque of blood elements.

AUTHOR.

Paterson, J. C.: Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries. Arch. Path. **22**: 313, 1936.

Vascularization of the intima of coronary arteries by discrete capillaries which arise from their lumens is a common finding in association with atherosclerosis. It is particularly marked in thrombosed coronary arteries. It has not been found in normal coronary arteries or in those affected by early nodular endarteritis.

Hemorrhagic lesions within the intima, which had occurred into atheromatous foci, have been observed in a number of arteriosclerotic coronary arteries, including those from nine consecutive patients with recent coronary thrombosis. When the hemorrhage was recent, capillary channels were found in the inner layers of the intima in close proximity to the extravasated blood. The sequence of events in the production of intimal hemorrhage appears to be (1) endarteritis with vascularization of the intima, (2) atheroma with resultant softening of the intercapillary stroma, and (3) capillary rupture. Because discrete intimal capillaries, atheroma, and intimal hemorrhage have been found in practically every coronary artery showing recent thrombosis in this series, it is suggested that these factors represent a chain of events which lead to thrombosis, the immediate cause being damage to the endothelium by the extravasation of blood into the intima.

AUTHOR.

Yater, Wallace M.: Demonstration of a Ruptured Popliteal Aneurysm by Thorium Dioxide Arteriography. South. M. J. **29**: 973, 1936.

Report of a case in which simple arterial and venous punctures, instead of aneurysmal puncture, were used to demonstrate an aneurysm radiographically. The aneurysm was well visualized. No danger in the use of direct aneurysmal puncture is implied.

H. M.

Böger, A., and Wezler, K.: The Elasticity of the Arterial "Windkessel" (Balloon) at Different Ages in Man. Ztschr. f. Kreislaufforsch. **28:** 554, 1936.

The elasticity coefficient of the *Windkessel* declines from its peak in childhood until the age of twenty-five years, and at that time a minimum is reached. It then increases again until the age of thirty-five years and remains constant thereafter. This is a result of interference between the growth curve on the one hand and the change in volume elasticity module of the arteries and the volume of the *Windkessel* on the other. The growth curve slows down after twenty years of age, the volume elasticity module changes most rapidly between the ages of twenty and thirty-five years, and the volume of the *Windkessel* keeps pace with the volume elasticity module. Methods are described for calculating these factors from measurements of pulse wave velocity of the aorta, the duration of the femoral pulse, and the x-ray cross-section of the aorta.

The *Windkessel* volume is smaller than the stroke volume of the heart and is consequently under considerable tension. The increase in length and cross-section of the *Windkessel* compensates for the loss of elasticity of the arterial wall with age and explains why the arterial pressure changes so little as the normal person grows up and senescence appears.

L. N. K.

Kramer, Kurt: Measurement of the Velocity of Blood Flow in Unopened Arteries. Arch. f. d. ges. Physiol. **238:** 91, 1936.

The method depends upon the use of a pair of photometers adapted by the author for registering changes in the oxygen saturation of the arterial blood. The instrument is very sensitive and rapid, and it records, when coupled with an electrically operated optical system, a curve of the fluctuations in oxygen content with each respiration. The photometers were connected, 10 to 15 cm. apart, with the femoral artery of a dog. Simultaneous records of the respiratory waves of oxygen saturation were obtained on a single piece of photographic paper, and the difference in time between similar points on the curves measured. The distance between the two photometers was measured, and the speed of the movement of blood was readily calculated as frequently as the rate of respiration permitted. He found velocities varying from 10 to 20 cm. per second in the femoral arteries of dogs narcotized with barbiturates. Two exceptionally good curves are reproduced. He realized that mixing of the blood in its forward movement might introduce an error, but, because the values obtained by gas analysis agreed so closely with those obtained from the photometer, such an error seemed unlikely. He could not, as he had hoped, calculate change in rate of blood flow because of simultaneous variations in the cross-section of the artery.

J. M. S.

Dorsey, John L.: Control of the Tobacco Habit. Ann. Int. Med. **10:** 628, 1936.

The consequences of abuse of tobacco are now being recognized and discussed in current medical literature. The ill effects of nicotine are believed to play a part in such conditions as peripheral vascular disease, organic and functional diseases of the stomach, pregnancy, headache, hyperglycemia, rhinitis, hypertension, asthma, cirrhosis of the liver, deafness, amblyopia, ether anesthesia, and others. Limitation of the use of tobacco seems much more difficult than the complete withdrawal. The use of lobelia or Indian tobacco is found to be effective in lessening the acute discomforts which result from the sudden withdrawal of tobacco. The drug is used in the form of lobeline sulphate, 0.008 gm. (1/8 gr.), given by mouth in capsule form immediately following a meal. This dose is repeated as often as the patient feels the urge to smoke.

E. A. H.